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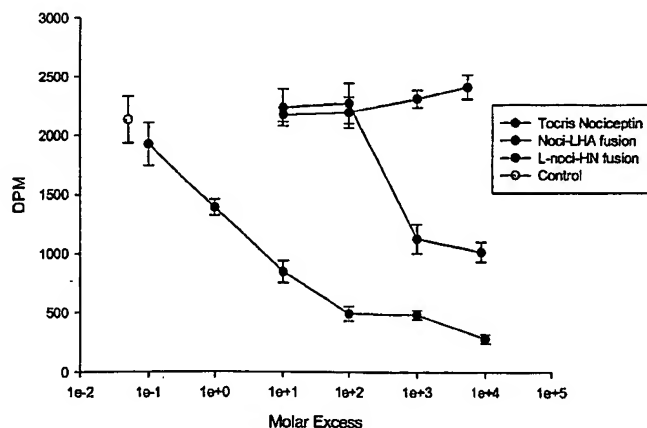
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(54) Title: Non-cytotoxic Protein Conjugates

Competition Assay : Nociceptin-LH₃/A Fusions
vs 1nM [³H]-Nociceptin on eDRGs (4°C)



(57) Abstract: A non-cytotoxic protein conjugate for inhibition or reduction of exocytic fusion in a nociceptive sensory afferent cell, comprising: (i) a Targeting Moiety (TM), wherein said TM is an agonist of a receptor present on said nociceptive sensory afferent cell, and wherein said receptor undergoes endocytosis to be incorporated into an endosome within the nociceptive sensory afferent cell; (ii) a non-cytotoxic protease or a fragment thereof, wherein the protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus of said nociceptive sensory afferent cell; and (iii) a Translocation Domain, wherein the Translocation Domain translocates the protease or protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the nociceptive sensory afferent cell. Nucleic acid sequences encoding the protein conjugates, methods of preparing same and uses thereof are also described.



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Non-cytotoxic Protein Conjugates

This invention relates to a non-cytotoxic protein conjugate, and to the use of said
5 conjugate for treating pain.

Toxins may be generally divided into two groups according to the type of effect that they have on a target cell. In more detail, the first group of toxins kill their natural target cells, and are therefore known as cytotoxic toxin molecules. This group of
10 toxins is exemplified *inter alia* by plant toxins such as ricin, and abrin, and by bacterial toxins such as diphtheria toxin, and *Pseudomonas* exotoxin A. Cytotoxic toxins typically kill their target cells by inhibiting the cellular process of protein synthesis.

15 In contrast, the second group of toxins, which are known as non-cytotoxic toxins, do not (as their name confirms) kill their natural target cells. Non-cytotoxic toxins have attracted much less commercial interest than have their cytotoxic counterparts, and exert their effects on a target cell by inhibiting cellular processes other than protein synthesis. As with their cytotoxic counterparts, non-cytotoxic toxins are produced
20 from a variety of sources such as plants, and bacteria. Bacterial non-cytotoxic toxins are now described in more detail.

Clostridial neurotoxins are proteins that typically have a molecular mass of the order of 150 kDa. They are produced by various species of bacteria, especially of the
25 genus *Clostridium*, most importantly *C. tetani* and several strains of *C. botulinum*, *C. butyricum* and *C. argentinense*. There are at present eight different classes of the clostridial neurotoxin, namely: tetanus toxin, and botulinum neurotoxin in its serotypes A, B, C₁, D, E, F and G, and they all share similar structures and modes of action.

30

Clostridial neurotoxins represent a major group of non-cytotoxic toxin molecules, and

are synthesised by the host bacterium as single polypeptides that are modified post-translationally by a proteolytic cleavage event to form two polypeptide chains joined together by a disulphide bond. The two chains are termed the heavy chain (H-chain), which has a molecular mass of approximately 100 kDa, and the light chain
5 (L-chain), which has a molecular mass of approximately 50 kDa.

L-chains possess a protease function (zinc-dependent endopeptidase activity) and exhibit high substrate specificity for vesicle and/or plasma membrane associated proteins involved in the exocytic process. L-chains from different clostridial species
10 or serotypes may hydrolyse different but specific peptide bonds in one of three substrate proteins, namely synaptobrevin, syntaxin or SNAP-25. These substrates are important components of the neurosecretory machinery.

Non-cytotoxic toxins are also produced by other bacteria, such as from the genus
15 *Neisseria*, most importantly from the species *N. gonorrhoeae*. For example, *Neisseria* sp. produces the non-cytotoxic toxin IgA protease (see WO99/58571).

It has been well documented in the art that toxin molecules may be re-targeted to a cell that is not the toxin's natural target cell. When so re-targeted, the modified toxin
20 is capable of binding to a desired target cell and, following subsequent translocation into the cytosol, is capable of exerting its effect on the target cell. Said re-targeting is achieved by replacing the natural Targeting Moiety (TM) of the toxin with a different TM. In this regard, the TM is selected so that it will bind to a desired target cell, and allow subsequent passage of the modified toxin into an endosome within
25 the target cell. The modified toxin also comprises a translocation domain to enable entry of the non-cytotoxic protease into the cell cytosol. The translocation domain can be the natural translocation domain of the toxin or it can be a different translocation domain obtained from a microbial protein with translocation activity.

30 For example, in the context of non-cytotoxic toxin molecules, it has been well documented that a clostridial neurotoxin may be re-targeted by incorporation of a Targeting Moiety (TM), which is not the natural TM of a clostridial neurotoxin. The

described chemical conjugation and recombinant methodologies are now regarded as conventional, and reference is made to Hermanson, G.T. (1996), Bioconjugate techniques, Academic Press, and to Wong, S.S. (1991), Chemistry of protein conjugation-and cross-linking, CRC Press.

5

For example, WO94/21300 describes modified clostridial neurotoxin molecules that are capable of regulating Integral Membrane Protein (IMP) density present at the cell surface of the target cell. The modified neurotoxin molecules are thus capable of controlling cell activity (e.g. glucose uptake) of the target cell. WO96/33273 and
10 WO99/17806 describe modified clostridial neurotoxin molecules that target peripheral sensory afferents. The modified neurotoxin molecules are thus capable of demonstrating an analgesic effect. WO00/10598 describes the preparation of modified clostridial neurotoxin molecules that target mucus hypersecreting cells (or neuronal cells controlling said mucus hypersecreting cells), which modified
15 neurotoxins are capable of inhibiting hypersecretion from said cells. WO01/21213 describes modified clostridial neurotoxin molecules that target a wide range of different types of non-neuronal target cells. The modified molecules are thus capable of preventing secretion from the target cells. Additional publications in the technical field of re-targeted toxin molecules include: WO00/62814; WO00/04926;
20 US5,773,586; WO93/15766; WO00/61192; and WO99/58571.

Thus, from the above-described publications, it will be appreciated that the basic concept of re-targeting a non-cytotoxic protease to a desired target cell, by selecting a TM that has a corresponding receptor present on the target cell, has been well
25 documented.

However, different receptors present on a target cell of interest demonstrate different binding affinities for different TMs. This may be a particular problem with pain-sensing cells, which possess a wide range of receptor types having different binding
30 affinities for different TMs. Thus, a re-targeted conjugate comprising a particular TM (that binds to a receptor on a pain-sensing cell) may demonstrate a low binding affinity for a pain-sensing target cell, which is undesirable.

There is therefore a need to develop modified non-cytotoxic conjugates that address one or more of the above problems. Of particular interest is the development of an improved conjugate for use in treating pain.

5

The present invention seeks to address one or more of the above problems by using as the conjugate's Targeting Moiety (TM) an "agonist" of a receptor that is present on the pain-sensing target cell of interest. In preferred embodiments, the pain-sensing target cell is a nociceptive sensory afferent, more preferably a primary
10 nociceptive sensory afferent. In particularly preferred embodiments, the TM is an agonist of the opioid-like receptor-1 (ORL₁) receptor.

Accordingly, in a first aspect, the present invention provides a non-cytotoxic conjugate for inhibition or reduction of exocytic fusion in a nociceptive sensory
15 afferent cell, comprising:

(i) a Targeting Moiety (TM),

20

wherein said TM is an agonist of a receptor present on said nociceptive sensory afferent cell, and wherein said receptor undergoes endocytosis to be incorporated into an endosome within the nociceptive sensory afferent cell;

(ii) a non-cytotoxic protease or a fragment thereof,

25

wherein the protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus of said nociceptive sensory afferent cell; and

30

(iii) a Translocation Domain,

wherein the Translocation Domain translocates the protease or

protease fragment from within the endosome, across the endosomal membrane, and into the cytosol of the nociceptive sensory afferent cell.

- 5 The use of an "agonist", which would normally stimulate a biological process, particularly exocytosis (for example, an increase in cellular secretion, or an up-regulation in membrane protein expression), is an exciting development in the technical field of re-targeted toxins. Furthermore, it is particularly surprising that an agonist may be employed in a therapeutic composition to achieve a reduction or
10 inhibition of a biological process that the agonist would normally stimulate.

The agonist-containing conjugates of the present invention represent a distinct subset of toxin conjugates. In more detail, the conjugates of the present invention comprise TMs that have been selected on the basis of specific agonist properties
15 rather than on the simple basis that they have a corresponding receptor on a pain-sensing target cell of interest.

Conventionally, an agonist has been considered any molecule that can either increase or decrease activities within a cell, namely any molecule that simply causes
20 an alteration of cell activity. For example, the conventional meaning of an agonist would include: a chemical substance capable of combining with a receptor on a cell and initiating a reaction or activity, or a drug that induces an active response by activating receptors, whether the response is an increase or decrease in cellular activity.

25

However, for the purposes of this invention, an agonist is more specifically defined as a molecule that is capable of stimulating the process of exocytic fusion in a pain-sensing target cell, which process is susceptible to inhibition by a protease (or fragment thereof) capable of cleaving a protein of the exocytic fusion apparatus in
30 said target cell.

Accordingly, the particular agonist definition of the present invention would exclude

many molecules that would be conventionally considered as agonists. For example, nerve growth factor (NGF) is an agonist in respect of its ability to promote neuronal differentiation via binding to a TrkA receptor. However, NGF is not an agonist when
5 assessed by the above criteria because it is not a principal inducer of exocytic fusion. In addition, the process that NGF stimulates (i.e. cell differentiation) is not susceptible to inhibition by the protease activity of a non-cytotoxic toxin molecule.

In use, an agonist-containing conjugate of the present invention does not deactivate an agonist receptor on a pain-sensing target cell, but rather the protease activity of
10 the conjugate serves to negate the agonist-mediated response.

Furthermore, once delivered to the cytosol of the pain-sensing target cell, the protease component of a conjugate of the present invention inhibits or blocks the action of all subsequent agonists capable of causing the same effect (i.e. increased
15 exocytic fusion) in the same target cell. This is advantageous and means that the conjugates of the present invention have application in situations where multiple agonists may be responsible for causing the sensation of pain. Thus, when designing a conjugate of the present invention, the TM that is selected for delivery need not necessarily be the principal agonist involved in causing the sensation of
20 pain.

Agonist-mediated delivery according to the present invention provides the following significant advantage over previous non-cytotoxic protease-containing therapeutics: use of an agonist may confer preferential binding and/or internalisation properties on
25 the conjugate. This, in turn, may result in more efficient delivery of the protease component to a pain-sensing target cell.

In addition, use of an agonist as a TM is self-limiting with respect to side-effects. In more detail, binding of an agonist to a pain-sensing target cell increases exocytic
30 fusion, which may exacerbate the sensation of pain. However, the exocytic process that is stimulated by agonist binding is subsequently reduced or inhibited by the protease component of the conjugate.

In preferred embodiments of the invention, the TM is an agonist of the ORL₁ receptor. The ORL₁ receptor is present on pain-sensing cells in the body.

5 The ORL₁ receptor is a member of the G-protein-coupled class of receptors, and has a seven transmembrane domain structure. The properties of the ORL₁ receptor are discussed in detail in Mogil & Pasternak (2001), *Pharmacological Reviews*, Vol. 53, No. 3, pages 381-415.

10 Throughout this specification, reference to the "ORL₁ receptor" embraces all members of the ORL₁ receptor family. Members of the ORL₁ receptor family typically have a seven transmembrane domain structure, and are coupled to G-proteins of the G_i and G_o families. A method for determining the G-protein-stimulating activity of ligands of the ORL₁ receptor is given in Example 17. A method for measuring
15 reduction in cellular cAMP levels following ORL₁ activation is given in Example 16. A further characteristic of members of the ORL₁ receptor family is that they are typically able to bind nociceptin (the natural ligand of ORL₁). As an example, all alternative splice variants of the ORL₁ receptor, are members of the ORL₁ receptor family.

20

The conjugates of the present invention generally demonstrate a reduced binding affinity (in the region of up to 100-fold) for nociceptive sensory afferent target cells when compared with the corresponding 'free' TM. However, despite this observation, the conjugates of the present invention surprisingly demonstrate good
25 efficacy. This can be attributed to two principal features. First, the non-cytotoxic protease component is catalytic – thus, the therapeutic effect of a few such molecules is rapidly amplified. Secondly, the receptors present on the nociceptive sensory afferents need only act as a gateway for entry of the therapeutic, and need not necessarily be stimulated to a level required in order to achieve a ligand-receptor
30 mediated pharmacological response. Accordingly, the conjugates of the present invention may be administered at a dosage that is much lower that would be employed for other types of analgesic molecules such as NSAIDS, morphine, and

gabapentin. The latter molecules are typically administered at high microgram to milligram (even up to hundreds of milligram) quantities, whereas the conjugates of the present invention may be administered at much lower dosages, typically at least 40-fold lower, and more typically at 100-fold lower.

5

In a particularly preferred embodiment of the invention, the TM of the conjugate is nociceptin - the natural ligand for the ORL₁ receptor. Nociceptin targets the ORL₁ receptor with high affinity.

10 Examples of other preferred TMs include:

Code	Sequence	Ref.	SEQ ID No.
Nociceptin 1-17	FGGFTGARKSARKLANQ	[1]	1,2
Nociceptin 1-11	FGGFTGARKSA	[1]	3,4
Nociceptin [Y10]1-11	FGGFTGARKYA	[1]	5,6
Nociceptin [Y11]1-11	FGGFTGARKSY	[1]	7,8
Nociceptin [Y14]1-17	FGGFTGARKSARKYANQ	[1]	9,10
Nociceptin 1-13	FGGFTGARKSARK	[2]	11,12
Nociceptin [R14K15] 1-17 (also known as "variant" nociceptin)	FGGFTGARKSARKRKNQ	[3,4]	13,14
Nociceptin 1-13-NH ₂	FGGFTGARKSARK-NH ₂	[5]	-
Nociceptin Phe (<i>p</i> -NO ₂) 1-17	(<i>p</i> NO ₂)FGGFTGARKSARKLANQ	[5]	-
Lofentanil	Non-peptide agonists	[5]	-

Code	Sequence	Ref.	SEQ ID No.
Etorphine	Non-peptide agonists	[5]	-
Peptide agonist	Peptide agonists from combinatorial library approach	[6]	-

[1] Mogil & Pasternak, 2001, Pharmacol. Rev., 53, 381-415

[2] Maile et al., 2003, Neurosci. Lett., 350, 190-192

[3] Rizzi et al., 2002, J. Pharmacol. Exp. Therap., 300, 57-63

5 [4] Okada et al., 2000, Biochem. Biophys. Res. Commun., 278, 493-498

[5] Zaveri, 2003, Life Sci., 73, 663-678.

[6] Dooley et al., 1997, J Pharmacol Exp Ther. 283(2), 735-41.

The TM preferably comprises a maximum of 50 amino acid residues, more preferably a maximum of 40 amino acid residues, particularly preferably a maximum of 30 amino acid residues, and most preferably a maximum of 20 amino acid residues. For example, nociceptin is a 17 amino acid residue peptide.

The above-identified "variant" TM demonstrates particularly good binding affinity (when compared with natural nociceptin) for nociceptive sensory afferents. Generally speaking, a TM-containing conjugate will demonstrate an approximate 100-fold reduction in binding ability *vis-à-vis* the TM *per se*. The above-mentioned "variant" TM *per se* demonstrates an approximate 3- to 10-fold increase in binding ability for a nociceptive sensory afferent *vis-à-vis* natural nociceptin. Thus, a "variant" TM-containing fusion might be expected to demonstrate an approximate 10-fold reduction in binding ability for a nociceptive sensory afferent *vis-à-vis* 'free' nociceptin. However, the present inventors have demonstrated that conjugates comprising said "variant" TM demonstrate a binding ability that (most surprisingly) closely mirrors that of 'free' nociceptin – see Figure 17.

25

In the context of the present invention, the term agonist of the ORL₁ receptor (such as nociceptin, or any one of the peptides listed in the table above) embraces

molecules having at least 70%, preferably at least 80%, more preferably at least 90%, and most preferably at least 95% homology with said agonist. The agonist homologues retain the agonist properties of nociceptin at the ORL₁ receptor, which may be tested using the methods provided in Example 10.

5

The invention also encompasses fragments, variants, and derivatives of any one of the TMs described above. These fragments, variants, and derivatives will substantially retain the properties that are ascribed to said TMs.

- 10 The agonist properties of a TM can be confirmed using the methods described in Example 1. These methods are based on previous experiments (see Inoue *et al.* (1998) Proc. Natl. Acad. Sci., 95, 10949-10953), which confirm that the natural agonist of the ORL₁ receptor, nociceptin, causes the induction of substance P release from nociceptive primary afferent neurons. This is supported by the facts
- 15 that:

- the nociceptin-induced responses are abolished by specific NK1 receptor (the substance P receptor) antagonists; and
- 20 ➤ pre-treatment of the cells with capsaicin (which depletes substance P from small diameter primary afferent neurons) attenuates the nociceptin-induced responses.

Similarly, Inoue *et al.* confirm that an intraplantar injection of botulinum neurotoxin type A abolishes the nociceptin-induced responses. Since it is known that BoNT

25 inhibits the release of substance P from primary afferent neurons (Welch *et al.*, (2000), Toxicon, 38, 245-258), this confirms the link between nociceptin-ORL₁ interaction and subsequent release of substance P.

- 30 Thus, a TM can be said to have agonist activity at the ORL₁ receptor if the TM causes an induction in the release of substance P from a nociceptive sensory afferent neuron (see Example 1).

In another embodiment, opioids represent a preferred group of TMs of the present invention. Within this family of peptides is included enkephalins (met and leu), endomorphins 1 and 2, β -endorphin and dynorphin. Opioid peptides are frequently
5 used in the clinic to modify the activity to nociceptors, and other cells involved in the pain response. As exemplified by the three-step World Health Organisation Analgesic Ladder, opioids have entry points into the pharmacological treatment of chronic cancer and non-cancer pain at all three stages, underlining their importance to the treatment of pain. Reference to opioids embraces fragments, variants and
10 derivatives thereof, which retain the ability to bind to nociceptive sensory afferents. The protease of the present invention embraces all naturally-occurring non-cytotoxic proteases that are capable of cleaving one or more proteins of the exocytic fusion apparatus in eukaryotic cells.

15 The protease of the present invention is preferably a bacterial protease.

More preferably, the bacterial protease is selected from the genera *Clostridium* or *Neisseria* (e.g. a clostridial L-chain, or a neisserial IgA protease preferably from *N. gonorrhoeae*).

20 The present invention also embraces modified non-cytotoxic proteases, which include amino acid sequences that do not occur in nature and/or synthetic amino acid residues, so long as the modified proteases still demonstrate the above-mentioned protease activity.

25 The protease of the present invention preferably demonstrates a serine or metalloprotease activity (e.g. endopeptidase activity). The protease is preferably specific for a SNARE protein (e.g. SNAP-25, synaptobrevin/VAMP, or syntaxin).

30 Particular mention is made to the protease domains of neurotoxins, for example the protease domains of bacterial neurotoxins. Thus, the present invention embraces the use of neurotoxin domains, which occur in nature, as well as recombinantly

prepared versions of said naturally-occurring neurotoxins.

Exemplary neurotoxins are produced by clostridia, and the term clostridial neurotoxin embraces neurotoxins produced by *G. tetani* (TeNT), and by *C. botulinum* (BoNT) serotypes A-G, as well as the closely related BoNT-like neurotoxins produced by *C. baratii* and *C. butyricum*. The above-mentioned abbreviations are used throughout the present specification. For example, the nomenclature BoNT/A denotes the source of neurotoxin as BoNT (serotype A). Corresponding nomenclature applies to other BoNT serotypes.

The term L-chain fragment means a component of the L-chain of a neurotoxin, which fragment demonstrates a metalloprotease activity and is capable of proteolytically cleaving a vesicle and/or plasma membrane associated protein involved in cellular exocytosis.

A Translocation Domain is a molecule that enables translocation of a protease (or fragment thereof) into a pain-sensing target cell such that a functional expression of protease activity occurs within the cytosol of the target cell. Whether any molecule (e.g. a protein or peptide) possesses the requisite translocation function of the present invention may be confirmed by any one of a number of conventional assays.

For example, Shone C. (1987) describes an *in vitro* assay employing liposomes, which are challenged with a test molecule. Presence of the requisite translocation function is confirmed by release from the liposomes of K^+ and/or labelled NAD, which may be readily monitored (see Shone C. (1987) Eur. J. Biochem; vol. 167(1): pp. 175-180).

A further example is provided by Blaustein R. (1987), which describes a simple *in vitro* assay employing planar phospholipid bilayer membranes. The membranes are challenged with a test molecule and the requisite translocation function is confirmed by an increase in conductance across said membranes (see Blaustein (1987) FEBS Letts; vol. 226, no. 1: pp. 115-120).

Additional methodology to enable assessment of membrane fusion and thus identification of Translocation Domains suitable for use in the present invention are provided by *Methods in Enzymology*, Vols. 220 and 221; Membrane Fusion
 5 Techniques, Parts A and B, Academic Press 1993.

The Translocation Domain is preferably capable of formation of ion-permeable pores in lipid membranes under conditions of low pH. Preferably, it has been found to use only those portions of the protein molecule capable of pore-formation within the
 10 endosomal membrane.

The Translocation Domain may be obtained from a microbial protein source, in particular from a bacterial or viral protein source. Hence, in one embodiment, the Translocation Domain is a translocating domain of an enzyme, such as a bacterial
 15 toxin or viral protein.

It is well documented that certain domains of bacterial toxin molecules are capable of forming such pores. It is also known that certain translocation domains of virally expressed membrane fusion proteins are capable of forming such pores. Such
 20 domains may be employed in the present invention.

The Translocation Domain may be of a clostridial origin, namely the H_N domain (or a functional component thereof). H_N means a portion or fragment of the H-chain of a clostridial neurotoxin approximately equivalent to the amino-terminal half of the H-chain, or the domain corresponding to that fragment in the intact H-chain. Examples
 25 of suitable clostridial Translocation Domains include:

	Botulinum type A neurotoxin	-	amino acid residues (449-871)
	Botulinum type B neurotoxin	-	amino acid residues (441-858)
30	Botulinum type C neurotoxin	-	amino acid residues (442-866)
	Botulinum type D neurotoxin	-	amino acid residues (446-862)
	Botulinum type E neurotoxin	-	amino acid residues (423-845)

Botulinum type F neurotoxin	-	amino acid residues (440-864)
Botulinum type G neurotoxin	-	amino acid residues (442-863)
Tetanus neurotoxin	-	amino acid residues (458-879)

- 5 For further details on the genetic basis of toxin production in *Clostridium botulinum* and *C. tetani*, we refer to Henderson *et al.* (1997) in *The Clostridia: Molecular Biology and Pathogenesis*, Academic press.

The term H_N embraces naturally-occurring neurotoxin H_N portions, and modified H_N portions having amino acid sequences that do not occur in nature and/or synthetic amino acid residues, so long as the modified H_N portions still demonstrate the above-mentioned translocation function.

- Alternatively, the Translocation Domain may be of a non-clostridial origin (see table below). Examples of non-clostridial Translocation Domain origins include, but are not restricted to, the translocation domain of diphtheria toxin [O'Keefe *et al.*, Proc. Natl. Acad. Sci. USA (1992) 89, 6202-6206; Silverman *et al.*, J. Biol. Chem. (1993) 269, 22524-22532; and London, E. (1992) *Biochem. Biophys. Acta.*, 1112, pp.25-51], the translocation domain of *Pseudomonas* exotoxin type A [Prior *et al.* Biochemistry (1992) 31, 3555-3559], the translocation domains of anthrax toxin [Blanke *et al.* Proc. Natl. Acad. Sci. USA (1996) 93, 8437-8442], a variety of fusogenic or hydrophobic peptides of translocating function [Plank *et al.* J. Biol. Chem. (1994) 269, 12918-12924; and Wagner *et al.* (1992) *PNAS*, 89, pp.7934-7938], and amphiphilic peptides [Murata *et al.* (1992) *Biochem.*, 31, pp.1986-1992].
- 25 The Translocation Domain may mirror the Translocation Domain present in a naturally-occurring protein, or may include amino acid variations so long as the variations do not destroy the translocating ability of the Translocation Domain.

Particular examples of viral Translocation Domains suitable for use in the present invention include certain translocating domains of virally expressed membrane fusion proteins. For example, Wagner *et al.* (1992) and Murata *et al.* (1992) describe the translocation (i.e. membrane fusion and vesiculation) function of a

- number of fusogenic and amphiphilic peptides derived from the N-terminal region of influenza virus haemagglutinin. Other virally expressed membrane fusion proteins known to have the desired translocating activity are a translocating domain of a fusogenic peptide of Semliki Forest Virus (SFV); a translocating domain of vesicular stomatitis virus (VSV) glycoprotein G, a translocating domain of SER virus F protein and a translocating domain of Foamy virus envelope glycoprotein. Virally encoded "spike proteins" have particular application in the context of the present invention, for example, the E1 protein of SFV and the G protein of VSV.
- 10 Use of the Translocation Domains (listed below) includes use of sequence variants thereof. A variant may comprise one or more conservative nucleic acid substitutions and/or nucleic acid deletions or insertions, with the proviso that the variant possesses the requisite translocating function. A variant may also comprise one or more amino acid substitutions and/or amino acid deletions or insertions, so long as
- 15 the variant possesses the requisite translocating function.

Translocation Domain source	Amino acid residues	References
Diphtheria toxin	194-380	Silverman <i>et al.</i> , 1994, J. Biol. Chem. 269, 22524-22532 London E., 1992, Biochem. Biophys. Acta., 1113, 25-51
Domain II of pseudomonas exotoxin	405-613	Prior <i>et al.</i> , 1992, Biochemistry 31, 3555-3559 Kihara & Pastan, 1994, Bioconj Chem. 5, 532-538
Influenza virus haemagglutinin	GLFGAIAGFIENGWE GMIDGWYG, and Variants thereof	Plank <i>et al.</i> , 1994, J. Biol. Chem. 269, 12918-12924 Wagner <i>et al.</i> , 1992, PNAS, 89, 7934-7938 Murata <i>et al.</i> , 1992, Biochemistry 31, 1986-1992

Translocation Domain source	Amino acid residues	References
Semliki Forest virus fusogenic protein	Translocation domain	Kielian <i>et al.</i> , 1996, J Cell Biol. 134(4), 863-872
Vesicular Stomatitis virus glycoprotein G	118-139	Yao <i>et al.</i> , 2003, Virology 310(2), 319-332
SER virus F protein	Translocation domain	Seth <i>et al.</i> , 2003, J Virol 77(11) 6520-6527
Foamy virus envelope glycoprotein	Translocation domain	Picard-Maureau <i>et al.</i> , 2003, J Virol. 77(8), 4722-4730

Once a potential receptor agonist (e.g. an ORL1 agonist) has been identified, one or more of the following optional steps may be carried out:

- 5 (A) confirming that the putative agonist molecule or agonist is capable of being combined with a non-cytotoxic protease (or a fragment thereof) and optionally a Translocation Domain to form a conjugate of the present invention; and/or
- 10 (B) confirming that said putative agonist molecule or agonist binds to the receptor on the pain-sensing target cell, which receptor is susceptible to receptor-mediated endocytosis; and/or
- 15 (C) confirming that said putative agonist molecule or agonist is able to deliver a non-cytotoxic protease (or fragment thereof) into the cytosol of a pain-sensing target cell.

The above steps (A)-(C) may be confirmed by routine tests that would be readily
20 available to a skilled person.

For example, step (A) may be performed by a simple chemical conjugation experiment using conventional conjugation reagents and/or linker molecules, followed by native polyacrylamide gel electrophoresis to confirm that a conjugate of ~~the present invention is formed that~~ has the anticipated molecular weight. The
5 conjugate components are typically linked together (optionally via linker molecules) by covalent bonds.

For example, step (B) may be performed by any one of a range of methodologies for assessment of binding of a ligand. Standard text, for example "Receptor-Ligand
10 Interactions. A Practical Approach. Ed. E. C. Hulme, IRL Press, 1992" are available that describe such approaches in detail. In brief, the agonist or putative agonist molecule is labelled (for example, with 125-iodine) and applied to a cell preparation *in vitro* in the presence of an excess of unlabelled agonist. The purpose of the unlabelled material is to saturate any non-specific binding sites. The agonist is
15 incubated with the cell preparation for sufficient time to achieve equilibrium, and the amount of label bound to the cells assessed by measuring cell associated radioactivity, for example by scintillation or gamma counting.

A further example involves gold-labelling of the agonist (or putative agonist),
20 followed by the use of electron microscopy to monitor the cellular transport progress of the labelled agonist [see the basic methodology described by Rabinowitz S. (1992); J. Cell. Biol. 116(1): pp. 95-112; and that described by van Deurs (1986); J. Cell. Biol. 102: pp. 37-47].

25 For example, step (C) may be performed by contacting the conjugate prepared in step (A) with a suitable target cell and assessing cleavage of the substrate. This is performed by extraction of the SNARE proteins, followed by Western blotting of SDS-PAGE-separated samples. Cleavage of substrate is indicative of delivery of the protease into the target cell. In this regard, cleavage may be monitored by
30 disappearance of substrate and/or appearance of cleavage product. A particularly useful antibody that selectively binds to the cleaved substrate product is described in WO95/33850.

Preparation of a conjugate according to the present invention is now discussed.

It is known in the art that the H_C portion of a neurotoxin molecule can be removed
5 from the other portion of the H-chain, known as H_N, such that the H_N fragment
remains disulphide linked to the L-chain of the neurotoxin providing a fragment
known as LH_N. Thus, in one embodiment of the present invention the LH_N fragment
of a neurotoxin is covalently linked, using linkages which may include one or more
spacer regions, to a TM.

10

In another embodiment of the invention, the H_C domain of a neurotoxin is mutated,
blocked or modified, e.g. by chemical modification, to reduce or preferably
incapacitate its ability to bind the neurotoxin to receptors at the neuromuscular
junction. This modified neurotoxin is then covalently linked, using linkages which
15 may include one or more spacer regions, to a TM.

In another embodiment of the invention, the H-chain of a neurotoxin, in which the H_C
domain is mutated, blocked or modified, e.g. by chemical modification, to reduce or
preferably incapacitate its native binding ability, is combined with the L-chain of a
20 different neurotoxin, or another protease capable of cleaving a protein of the
exocytic fusion apparatus (e.g. IgA protease of *N. gonorrhoeae*). This hybrid,
modified neurotoxin is then covalently linked, using linkages which may include one
or more spacer regions, to a TM.

25 In another embodiment of the invention, the H_N domain of a neurotoxin is combined
with the L-chain of a different neurotoxin, or another protease capable of cleaving a
protein of the exocytic fusion apparatus (e.g. IgA protease of *N. gonorrhoeae*). This
hybrid is then covalently linked, using linkages which may include one or more
spacer regions, to a TM.

30

In another embodiment of the invention, the protease (for example the L-chain
component of a neurotoxin) is covalently linked, using linkages that may include one

or more spacer regions, to a TM that can also effect the internalisation of the protease into the cytoplasm of the relevant target cell(s).

5 In another embodiment of the invention, the protease (for example the L-chain component of a neurotoxin) is covalently linked, using linkages which may include one or more spacer regions, to a translocation domain to effect transport of the protease fragment into the cytosol.

10 In use, the domains of a conjugate according to the present invention are associated with each other. In one embodiment, two or more of the domains may be joined together either directly (e.g. by a covalent linkage), or via a linker molecule.

A variety of different linker/ spacer molecules may be employed in any of the fusion proteins of the present invention. Examples of such spacer molecules include those
15 illustrated in Figures 31 and 32. Particular mention here is made to GS15, GS20, GS25, and Hx27 – see Figures 31 and 32.

The present inventors have unexpectedly found that non-cytotoxic protease-TM conjugates (eg. CPNv/A) may demonstrate an improved binding activity for
20 nociceptive sensory afferents when the size of the spacer is selected so that (in use) the TM (preferably the C-terminus thereof) and the translocation domain (preferably the N-terminus thereof) are separated from one another by 40-105 angstroms, preferably by 50-100 angstroms, and more preferably by 50-90 angstroms. In another embodiment, the preferred spacers have an amino acid sequence of 11-29
25 amino acid residues, preferably 15-27 amino acid residues, and more preferably 20-27 amino acid residues. Suitable spacers may be routinely identified and obtained according to Crasto, C.J. and Feng, J.A. (2000) May, 13(5), pp. 309-312 – see also <http://www.fccc.edu/research/labs/feng/linker.html>.

30 Conjugation techniques suitable for use in the present invention have been well documented and are routine for a person skilled in the art.

The methodology involved in coupling two protein molecules (A and B) together is simple, and is achieved through the use of a cross-linking agent (also known as a chemical coupling agent). For example, molecules A and B are separately contacted with a cross-linking agent, which chemically modifies a specific surface group on each of molecules A and B thereby forming derivatised molecules A' and B'. The modified surface group on molecule A' is capable of covalently bonding with the modified surface group on molecule B'. Thus, the coupling reaction is completed by mixing together the two protein molecules A' and B'.

- 10 Chemical conjugation is illustrated by reference to the following embodiments, where P = non-cytotoxic protease component, T = translocation component, and TM = targeting moiety.

In one embodiment, a single chain P – T is prepared, which is then conjugated to a TM. In another embodiment, a single chain TM – T (or T – TM) is prepared, which is then conjugated to a P. In a further embodiment, a single chain P – TM (or TM – P) is prepared, which is then conjugated to a T. Another particularly preferred conjugate has the structure P – TM – T (with an optional protease cleavage site between P and TM).

20

Where the T and P components are prepared as a single chain polypeptide, a protease cleavage site is typically included between said components. Any protease cleavage site may be employed in this regard.

- 25 In an alternative embodiment, the three components may be simultaneously or sequentially conjugated together. Thus, the conjugation may be a one- or two-step process, and may include one or more different coupling agents.

Chemical coupling agents and cross-linking agents have been commercially available for many years.

30

Example 5 of the present invention describes in detail the use of one such coupling

agent, namely SPDP, to chemically couple two protein molecules (nociceptin, and the LH_N of botulinum neurotoxin). The two molecules are separately contacted with SPDP, and then mixed together to allow covalent conjugation.

- 5 The conjugate described in Example 6 confirms that another coupling agent, PDPH/EDAC, or Traut's reagent, may be employed as an alternative coupling agent to SPDP.

SPDP and Traut's reagent are popular and well-documented coupling agents in the technical field of protein conjugation chemistry and are presented here simply as two
10 examples of a well known class of compounds that may be employed to covalently link together the Targeting Moiety component and the clostridial neurotoxin component of the conjugate of the present invention. Other suitable agents include SMPB, SMCC (succinimidyl 4-(N-maleimidomethyl) cyclohexan-1-carboxylate), and
15 LC-SPDP.

In more detail, commercially available members of the well-known coupling agents may be used for conjugation purposes to produce a conjugate of the invention. Details of such agents can be found in the following publications:

20

Hermanson, G.T. (1996), Bioconjugate techniques, Academic Press;

Wong, S.S. (1991), Chemistry of protein conjugation and cross-linking, CRC Press;

25

Thorpe et al (1987), Cancer Res, 1987, 47, 5924-31. This paper describes the use of SMBT (sodium S-4-succinimidylloxycarbonyl-alpha-methyl benzyl thiosulfate) and SMPT (4-succinimidylloxycarbonyl-alpha-methyl-alpha(2-pyridyldithio)toluene);

30

and

Peeters et al (1989), J Immunol Methods. 1989, 120, 133-43. This

paper describes the use of 4 coupling reagents, MHS (succinimidyl 6-(N-maleimido)-n-hexanoate), SMCC (succinimidyl 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate), MBS (succinimidyl m-maleimidobenzoate), and SPDP.

5

The conjugates according to the present invention may also be prepared recombinantly, as detailed in Examples 9 to 12.

10 In one embodiment, the preparation of a recombinant conjugate involves arrangement of the coding sequences of a selected TM, a selected non-cytotoxic protease component, and a translocation component (in any order) in a single genetic construct. These coding sequences may be arranged in-frame so that subsequent transcription and translation is continuous through both coding sequences and results in a fusion protein. All constructs would have a 5' ATG codon
15 to encode an N-terminal methionine, and a C-terminal translational stop codon.

Thus, the recombinant preparation method results in the generation of a single chain polypeptide. In order to activate this polypeptide, a protease cleavage site is present between the non-cytotoxic protease component and the translocation component.
20 Cleavage of this site generates a di-chain polypeptide in which the protease and translocation domains are linked together by way of a covalent bond, preferably a disulphide bond. In this regard, any protease cleavage site may be employed.

In the single polypeptide aspect of the present invention, the TM is preferably either
25 N- or C-terminally located with respect to the fusion protein. In other words, it is preferred that the TM is not located between the P and T components of the single polypeptide fusion protein. In a particularly preferred embodiment, the TM is N-terminally located with respect to the fusion protein.

30 In one embodiment, an L-chain of a clostridial neurotoxin or another protease capable of cleaving a protein of the exocytic fusion apparatus (e.g. an IgA protease), or a fragment/variant thereof, may be expressed recombinantly as a fusion protein.

with a TM, which TM can also effect the internalisation of the L-chain component into the cytoplasm of the relevant target cell(s) responsible for secretion. Alternatively, the fusion protein may further comprise a Translocation Domain. The expressed fusion protein may include one or more spacer regions.

5

By way of example, the following information is required to produce, recombinantly, an agent of the present invention:

- (I) DNA sequence data relating to a selected TM;
- 10 (II) DNA sequence data relating to the protease component;
- (III) DNA sequence data relating to the translocation domain; and
- (IV) a protocol to permit construction and expression of the construct comprising (I), (II) and (III).

15 All of the above basic information (I)-(IV) are either readily available, or are readily determinable by conventional methods. For example, both WO98/07864 and WO99/17806 exemplify recombinant technology suitable for use in the present application.

20 In addition, methods for the construction and expression of the constructs of the present invention may employ information from the following references and others:

25 Lorberboum-Galski, H., FitzGerald, D., Chaudhary, V., Adhya, S., Pastan, I. (1988), Cytotoxic activity of an interleukin 2-Pseudomonas exotoxin chimeric protein produced in *Escherichia coli*. *Proc.Natl. Acad. Sci. USA*, 85(6):1922-6;

30 Murphy, J.R. (1988), Diphtheria-related peptide hormone gene fusions: a molecular genetic approach to chimeric toxin development. *Cancer Treat. Res.*; 37:123-40;

Williams, D.P., Parker, K., Bacha, P., Bishai, W., Borowski, M.,

Genbauffe, F., Strom, T.B., Murphy, J.R. (1987), Diphtheria toxin receptor binding domain substitution with interleukin-2: genetic construction and properties of a diphtheria toxin-related interleukin-2 fusion protein. *Protein Eng*;1(6):493-8;

5

Arora, N., Williamson, L.C., Leppla, S.H., Halpern, J.L. (1994), Cytotoxic effects of a chimeric protein consisting of tetanus toxin light chain and anthrax toxin lethal factor in non-neuronal cells *J. Biol. Chem.*, 269(42):26165-71;

10

Brinkmann, U., Reiter, Y., Jung, S.H., Lee, B., Pastan, I. (1993), A recombinant immunotoxin containing a disulphide-stabilized Fv fragment. *Proc. Natl. Acad. Sci. USA*, 90(16):7538-42; and

15

---O'Hare, M., Brown, A.N., Hussain, K., Gebhardt, A., Watson, G., Roberts, L.M., Vitetta, E.S., Thorpe, P.E., Lord, J.M. (1990), Cytotoxicity of a recombinant ricin-A-chain fusion protein containing a proteolytically-cleavable spacer sequence. *FEBS Lett* Oct 29;273(1-2):200-4.

20

Suitable clostridial neurotoxin sequence information relating to L- and L_HN-chains may be obtained from, for example, Kurazono, H. (1992) *J. Biol. Chem.*, vol. 267, No. 21, pp.14721-14729; and Popoff, M.R., and Marvaud, J.-C. (1999) *The Comprehensive Sourcebook of Bacterial Protein Toxins*, 2nd edition (ed. Alouf, J.E., and Freer, J.H.), Academic Press, pp.174-201.

25

All of the aforementioned publications are hereby incorporated into the present specification by reference thereto.

30

Similarly, suitable TM sequence data are widely available in the art. Alternatively, any necessary sequence data may be obtained by techniques which are well-known to the skilled person.

For example, DNA encoding the TM component may be cloned from a source organism by screening a cDNA library for the correct coding region (for example by using specific oligonucleotides-based on the known sequence information to probe the library), isolating the TM DNA, sequencing this DNA for confirmation purposes, and then placing the isolated DNA in an appropriate expression vector for expression in the chosen host.

As an alternative to isolation of the sequence from a library, the available sequence information may be employed to prepare specific primers for use in PCR, whereby the coding sequence is then amplified directly from the source material and, by suitable use of primers, may be cloned directly into an expression vector.

Another alternative method for isolation of the coding sequence is to use the existing sequence information and synthesise a copy, possibly incorporating alterations, using DNA synthesis technology. For example, DNA sequence data may be generated from existing protein and/or RNA sequence information. Using DNA synthesis technology to do this (and the alternative described above) enables the codon bias of the coding sequence to be modified to be optimal for the chosen expression host. This may give rise to superior expression levels of the fusion protein.

Optimisation of the codon bias for the expression host may be applied to the DNA sequences encoding the TM and clostridial components of the construct. Optimisation of the codon bias is possible by application of the protein sequence into freely available DNA/protein database software, e.g. programs available from Genetics Computer Group, Inc.

Having prepared a conjugate of the invention, it is a matter of routine to confirm that the various domains have retained their specified function.

Protease function after conjugation may be tested by using, for example, any one of

the following routine tests:

SNAP-25 (or synaptobrevin, or syntaxin) may be challenged with a conjugate to be tested, and then analysed by SDS-PAGE peptide separation techniques.
5 Subsequent detection of peptides (e.g. by silver staining) having molecular weights corresponding to the cleaved products of SNAP-25 (or other component of the neurosecretory machinery) would confirm the presence of a functional L-chain.

As a further alternative, the conjugate may be tested by assaying for SNAP-25 (or
10 synaptobrevin, or syntaxin) cleavage products via antibody-specific binding (see WO95/33850). In more detail, a specific antibody is employed for detecting cleavage of SNAP-25. Since the antibody recognises cleaved SNAP-25, but not uncleaved SNAP-25, identification of the cleaved product by the antibody confirms the presence of L-chain proteolytic function. By way of exemplification, such a
15 method is described in Examples 2 and 3 of WO96/33273.

Translocation component function after conjugation may be tested using, for example, any one of the following routine tests:

20 Suitable methods are, for example, described by Shone *et al.* (1987) Eur. J. Biochem. 167, pp.175-180; and by Blaustein *et al.* (1987) FEBS 226 (1), pp.115-120.

The Shone *et al.* method employs artificial liposomes loaded with potassium
25 phosphate buffer (pH 7.2) and radiolabelled NAD. Release of K⁺ and NAD from the liposomes correlates with a positive result for channel forming activity and hence translocation activity. In this regard, K⁺ release from liposomes may be measured using an electrode and NAD release calculated by measuring the radioactivity in the supernatant (see page 176, column 1, line 33 - column 2, line 17).

30

The Blaustein *et al.* method employs planar phospholipid bilayer membranes, which
are used to test for channel forming activity. In more detail, salt solutions on either

side of the membrane are buffered at a different pH - on the cis side, pH 4.7 or 5.5 and on the trans side, pH 7.4. The "conjugate" to be tested is added to the cis side of the membrane and electrical measurements are made under voltage clamp conditions, in order to monitor the flow of current across the membrane (see paragraph 2.2, pages 116-118). The presence of an active translocation function is confirmed by a steady rate of channel turn-on (i.e. a positive result for channel formation) -see paragraph 3, page 118.

Targeting Moiety (TM) function after conjugation may be tested by assaying for the agonist function inherent to the TM. Suitable methods include those described in Example 1.

The ability of the conjugate of the invention to inhibit substance P release from nociceptive afferent cells can be assessed using the methods described in Example 15.

In Example 15, a nociceptin-LHN/A conjugate according to the first aspect of the invention is assessed for its ability to inhibit the release of substance P from primary nociceptive sensory afferent neurons. As can be seen from Table 1, incubation of the conjugate with cultures of nociceptive afferent neurons results in a significant inhibition of release of substance P (when compared to incubation of the cells with LHN/A alone). The experiment therefore confirms that the conjugate is inhibiting substance P release from these cells.

In use of the present invention, a pain-sensing target cell is selected in which it is desired to reduce or inhibit the process of exocytic fusion, which exocytic process contributes to the symptoms associated with the sensation of pain. For example, the target cell in question may demonstrate an undesirable phenotype (e.g. an undesirable secretion, or the expression of an undesirable concentration of membrane receptor, transporter or membrane channel), which contributes to the symptoms associated with pain. Alternatively, a target cell may be selected in which the process of exocytic fusion contributes to the sensation of pain.

In preferred embodiments of the invention, the target cell is a nociceptive sensory afferent cell, preferably a primary nociceptive afferent cell (e.g. an A-fibre such as an A δ -fibre or a C-fibre). -Thus, the conjugates of the present invention are capable of inhibiting neurotransmitter or neuromodulator (e.g. glutamate, substance P, calcitonin-gene related peptide (CGRP), and/or neuropeptide Y) release from discrete populations of nociceptive sensory afferent neurons. In use, the conjugates reduce or prevent the transmission of sensory afferent signals (e.g. neurotransmitters or neuromodulators) from peripheral to central pain fibres, and therefore have application as therapeutic molecules for the treatment of pain, in particular chronic pain.

It is routine to confirm that a TM binds to a nociceptive sensory afferent. For example, a simple radioactive displacement experiment may be employed in which tissue or cells representative of the nociceptive sensory afferent (for example DRGs) are exposed to labelled (e.g. tritiated) ligand in the presence of an excess of unlabelled ligand. In such an experiment, the relative proportions of non-specific and specific binding may be assessed, thereby allowing confirmation that the ligand binds to the nociceptive sensory afferent target cell. Optionally, the assay may include one or more binding antagonists, and the assay may further comprise observing a loss of ligand binding. Examples of this type of experiment can be found in Hulme, E.C. (1990), Receptor-binding studies, a brief outline, pp 303-311, in Receptor biochemistry, A Practical Approach, Ed. E.C. Hulme, Oxford University Press.

According to a second aspect, the present invention provides a non-cytotoxic conjugate for inhibition or reduction of exocytotic fusion in a nociceptive sensory afferent cell, comprising:

(i) a Targeting Moiety (TM),

wherein said TM is an agonist of a receptor that is present on

said nociceptive sensory afferent cell, and wherein said receptor undergoes endocytosis to be incorporated into an endosome within the nociceptive sensory afferent cell;

- 5 (ii) a DNA sequence encoding a non-cytotoxic protease or a fragment thereof,

wherein the DNA sequence is expressible in the nociceptive sensory afferent cell and when so expressed provides a
10 protease or protease fragment capable of cleaving a protein of the exocytic fusion apparatus of said nociceptive sensory afferent cell; and

- (iii) a Translocation Domain,

15 wherein the Translocation Domain translocates the DNA sequence encoding the protease or protease fragment from within the endosome, across the endosomal membrane, and into the nociceptive sensory afferent cell.

20

In a preferred embodiment, the receptor is an ORL₁ receptor.

DNA encoding a protein of interest can be transfected into eukaryotic cells through receptor-mediated endocytosis of a protein-DNA conjugate, as confirmed by Cotton
25 *et al.* (Cotton, M., Wagner, E. and Birnstiel, L. (1993) Receptor-mediated transport of DNA into eukaryotic cells. *Methods in Enzymol.* 217, 619-645). Several methods exist for condensing DNA to a suitable size using polycationic ligands. These include: polylysine, various cationic peptides and cationic liposomes. Of these, polylysine was used in the present study because of its successfully reported use in
30 receptor-mediated transfection studies (Cotton *et al.*, 1993).

The DNA sequence encoding the non-cytotoxic protease component may be

expressed under the control of an operably linked promoter present as part of the agent (e.g. as part of the protease DNA sequence upstream of the coding region). Alternatively, expression of the protease component in the target cell may rely on a promoter present in the target cell.

5

The DNA sequence encoding the protease component may integrate into a DNA sequence of the target cell. One or more integration site(s) may be provided as part of the conjugate (e.g. as part of the protease DNA sequence).

10 The TM, Translocation Domain and protease components of this second aspect of the invention are as defined for the first aspect of the invention. Examples 13 and 14 describe the preparation of conjugates according to the second aspect of the invention.

15 According to a third aspect, the present invention provides a pharmaceutical composition comprising a conjugate according to the first and/or second aspect of the present invention.

The pharmaceutical composition may further comprise a pharmaceutically-
20 acceptable carrier, and/or a suitable diluent and/or excipient, although the exact form of the composition may be tailored to the mode of administration. Administration is preferably to a mammal, more preferably to a human.

The components of the composition may, for example, be employed in the form of
25 an aerosol or nebulisable solution for inhalation or a sterile solution for parenteral administration, intra-articular administration or intra-cranial administration.

The composition may also be administered by i.v. injection, which includes the use of pump systems. Spinal injection (e.g. epidural or intrathecal) or indwelling pumps
30 may also be used.

The dosage ranges for administration of the components of the present invention are

those to produce the desired therapeutic effect. It will be appreciated that the dosage range required depends on the precise nature of the components, the route of administration, the nature of the formulation, the age of the patient, the nature, extent or severity of the patient's condition, contraindications, if any, and the judgement of the attending physician.

Suitable daily dosages (for each component) are in the range 0.0001-1 mg/kg, preferably 0.0001-0.5 mg/kg, more preferably 0.002-0.5 mg/kg, and particularly preferably 0.004-0.5 mg/kg. The unit dosage can vary from less than 1 microgram to 30 mg, but typically will be in the region of 0.01 to 1 mg per dose, which may be administered daily or preferably less frequently, such as weekly or six monthly.

A particularly preferred dosing regimen is based on 2.5 ng of fusion protein (e.g. CPNv/A) as the 1X dose. In this regard, preferred dosages are in the range 1X-100X (i.e. 2.5-250 ng). This dosage range is significantly lower (i.e. at least 10-fold, typically 100-fold lower) than would be employed with other types of analgesic molecules such as NSAIDs, morphine, and gabapentin. Moreover, the above-mentioned difference is considerably magnified when the same comparison is made on a molar basis – this is because the fusion proteins of the present invention have a considerably greater Mw than do conventional 'small' molecule therapeutics.

Wide variations in the required dosage, however, are to be expected depending on the precise nature of the components, and the differing efficiencies of various routes of administration. For example, oral administration would be expected to require higher dosages than administration by intravenous injection.

Variations in these dosage levels can be adjusted using standard empirical routines for optimisation, as is well understood in the art.

Compositions suitable for injection may be in the form of solutions, suspensions or emulsions, or dry powders which are dissolved or suspended in a suitable vehicle prior to use.

Fluid unit dosage forms are typically prepared utilising a pyrogen-free sterile vehicle.

~~The active ingredients, depending on the vehicle and concentration used, can be~~
5 either dissolved or suspended in the vehicle.

Solutions may be used for all forms of parenteral administration, and are particularly used for intravenous injection. In preparing solutions the components can be dissolved in the vehicle, the solution being made isotonic if necessary by addition of
10 sodium chloride and sterilised by filtration through a sterile filter using aseptic techniques before filling into suitable sterile vials or ampoules and sealing. Alternatively, if solution stability is adequate, the solution in its sealed containers may be sterilised by autoclaving.

15 Advantageously additives such as buffering, solubilising, stabilising, preservative or bactericidal, suspending or emulsifying agents and/or local anaesthetic agents may be dissolved in the vehicle.

Dry powders which are dissolved or suspended in a suitable vehicle prior to use may
20 be prepared by filling pre-sterilised drug substance and other ingredients into a sterile container using aseptic technique in a sterile area.

Alternatively the components of the composition may be dissolved in an aqueous vehicle, the solution is sterilized by filtration and distributed into suitable containers
25 using aseptic technique in a sterile area. The product is then freeze-dried and the containers are sealed aseptically.

Parenteral suspensions, suitable for intramuscular, subcutaneous or intradermal injection, are prepared in substantially the same manner, except that the sterile
30 components are suspended in the sterile vehicle, instead of being dissolved and sterilisation cannot be accomplished by filtration. The components may be isolated

in a sterile state or alternatively it may be sterilised after isolation, e.g. by gamma

irradiation.

Advantageously, a suspending agent for example polyvinylpyrrolidone is included in the composition(s) to facilitate uniform distribution of the components.

5

Compositions suitable for administration via the respiratory tract include aerosols, nebulisable solutions or microfine powders for insufflation. In the latter case, particle size of less than 50 microns, especially less than 10 microns, is preferred. Such compositions may be made up in a conventional manner and employed in conjunction with conventional administration devices.

10

The compositions described in this invention can be used in vivo, either directly or as a pharmaceutically acceptable salt, for the treatment of conditions involving exocytosis (for example secretion, or the delivery of proteins such as receptors, transporters, and membrane channels to the plasma membrane of a cell).

15

According to a fourth aspect, the present invention provides a DNA construct that encodes a conjugate according to the first or second aspects of the invention.

By expressing the construct in a host cell, conjugates of the invention may be prepared.

20

According to a fifth aspect, the present invention provides a method of treatment of pain by administration to a patient of a conjugate, composition, or construct according to the first to fourth aspects of the invention, or any combination thereof.

25

In a preferred embodiment, the invention provides a method of treating chronic pain.

According to a sixth aspect, the present invention provides for the use of a conjugate, composition or construct according to the first to fourth aspects of the invention, for the manufacture of a medicament for treating pain, preferably chronic

30

pain.

Definitions Section

Exocytic fusion is a process by which intracellular molecules are transported from the cytosol of a pain-sensing target cell to the plasma (i.e. cell) membrane thereof. Thereafter, the intracellular molecules may become displayed on the outer surface of the plasma membrane, or may be secreted into the extracellular environment.

In a healthy individual, the rate of exocytic fusion is carefully regulated and allows control of the transport of molecules between the cytosol and the plasma membrane of a pain-sensing cell. For example, regulation of the exocytic cycle allows control of the density of receptors, transporters, or membrane channels present at the cell's surface, and/or allows control of the secretion rate of intracellular components (e.g. neurotransmitters) from the cytosol of the cell.

However, in an unhealthy individual, the regulation of exocytic fusion may be modified. For example, exocytic fusion may cause affected pain-sensing cells to enter a state of hypersecretion. Alternatively, exocytic fusion may result in the display of an increased concentration of receptors, transporters, or membrane channels present on the surface of the pain-sensing, which may expose the cell to undesirable external stimuli. Thus, the process of exocytic fusion may contribute to the progression and/or severity of pain, and therefore provides a target for therapeutic intervention.

It should also be appreciated that otherwise normal rates of cellular exocytic fusion may contribute to the progression and severity of pain in compromised patients. Thus, by targeting exocytic fusion in accordance with the present invention, it is also possible to provide therapy in such patients

Targeting Moiety (TM) means any chemical structure associated with a conjugate that functionally interacts with a receptor, e.g. an ORL₁ receptor, to cause a physical association between the conjugate and the surface of a pain-sensing target cell.

The term TM embraces any molecule (i.e. a naturally occurring molecule, or a chemically/physically modified variant thereof) that is capable of binding to a receptor on the target cell, which receptor is capable of internalisation (e.g. endosome-formation)—also-referred-to as-receptor-mediated-endocytosis. The TM
5 may possess an endosomal membrane translocation domain, in which case separate TM and Translocation Domain components need not be present in an agent of the present invention.

The term “fragment” means a peptide having at least thirty-five, preferably at least
10 twenty-five, more preferably at least fifteen, and most preferably at least ten amino acid residues of the TM in question. In one embodiment, the first amino acid residue of the fragment is the N-terminal amino acid residue of the TM from which the fragment has been derived.

15 An example of a “variant” is a peptide or peptide fragment of a TM that contains one or more analogues of an amino acid (e.g. an unnatural amino acid), or a substituted linkage.

A “derivative” comprises the TM in question, and a further peptide sequence. The
20 further peptide sequence should preferably not interfere with the basic folding and thus conformational structure of the TM. Two or more peptides (or fragments, or variants) may be joined together to form a derivative. Alternatively, a peptide (or fragment, or variant) may be joined to an unrelated molecule (e.g. a second, unrelated peptide). Derivatives may be chemically synthesized, but will be typically
25 prepared by recombinant nucleic acid methods. Additional components such as lipid, and/or polysaccharide, and/or polyketide components may be included.

The term non-cytotoxic means that the protease molecule in question does not kill the pain-sensing target cell to which it has been re-targeted.

30

The “protease cleavage site” of the present invention allows cleavage (preferably controlled cleavage) of the conjugate at a position between the non-cytotoxic

protease component and the TM component. In one embodiment, the conjugate may include more than one proteolytic cleavage site. However, where two or more such sites exist, they are different, thereby substantially preventing the occurrence of multiple cleavage events in the presence of a single protease. In another embodiment, it is preferred that the conjugate has a single protease cleavage site. The protease cleavage sequence(s) may be introduced (and/or any inherent cleavage sequence removed) at the DNA level by conventional means, such as by site-directed mutagenesis. Screening to confirm the presence of cleavage sequences may be performed manually or with the assistance of computer software (e.g. the MapDraw program by DNASTAR, Inc.).

Whilst any protease cleavage site may be employed, the following are preferred:

	Enterokinase	(DDDDK↓)
15	Factor Xa	(IEGR↓ / IDGR↓)
	TEV(Tobacco Etch virus)	(ENLYFQ↓G)
	Thrombin	(LVPR↓GS)
	PreScission	(LEVLFQ↓GP).

Also embraced by the term protease cleavage site is an intein, which is a self-cleaving sequence. The self-splicing reaction is controllable, for example by varying the concentration of reducing agent present.

The present invention is now described by reference to the following Examples and Figures, without intended limitation thereto.

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Figure 29 *In vitro* SNAP-25 cleavage in a DRG cell model

Figure 30 Expressed / purified CPNV-A-FXa-HT (removable his-tag)

Figure 31 *In vitro* efficacy of LC/A-nociceptin-H_N/A fusion proteins with variable spacer length, as assessed by ligand competition assay

5 Figure 32 *In vitro* efficacy of LC/A-nociceptin-H_N/A fusion proteins with variable spacer length, as assessed by *in vitro* SNAP-25 cleavage

The Figures are now described in more detail.

10 **Figure 1 - Expression and purification of recLH_N/B fusion protein**

SDS-PAGE analysis of expression and purification of recLH_N/B from *E. coli*. In Figure 1, recLH_N/B is purified from cell paste using a three column strategy as described in Example 3. Protein samples are separated by SDS-PAGE and
15 visualised by staining with simplyblue safestain coomassie reagent. Crude, soluble MBP-LH_N/B fusion protein contained within the clarified extract (lane 2) is loaded onto Q-Sepharose FF anion-exchange resin. Lane 3 represents recombinant MBP-LH_N/B fusion eluted from column at 150-200 mM salt. This sample is treated with factor Xa protease to remove MBP affinity tag (lane 4), and cleaved mixture diluted
20 to lower salt concentration prior to loading onto a Q-Sepharose FF anion-exchange column. Material eluted between 120-170 mM salt was rich in LH_N/B (lane 5). Protein in lanes 6 and 8 represents LH_N/B harvested after treatment with enterokinase and final purification using Benzamidine Sepharose, under non-reducing and reducing conditions respectively. Lanes 1 and 7 represent molecular
25 mass markers [Mark 12 (Invitrogen)].

Figure 2 - Expression and purification of LH_N/C fusion protein

SDS-PAGE analysis of expression and purification of LH_N/C from *E. coli*. In Figure
30 2, recLH_N/C is purified from *E. coli* cell paste using a two-step strategy described in Example 4. Protein samples are separated by SDS-PAGE and visualised by staining with coomassie blue. Clarified Crude cell lysate (lane 2) is loaded onto Q-

Sepharose FF anion-exchange resin. Fusion protein, MBP-LH_N/C is eluted with 0.1 M NaCl (lane 3). Eluted material incubated at 22°C for 16 h with factor Xa protease (New England Biolabs) to cleave fusion tag MBP and nick recLH_N/C at the linker site. The protein of interest is further-purified from cleaved fusion products (lane 4) using Q-Sepharose FF. Lanes 5 and 7 show purified recLH_N/C under non-reducing conditions and reduced with 10 mM DTT respectively, to illustrate disulphide bonding at the linker region between LC and H_N domains after nicking with factor Xa. Lanes 1 and 6 represent molecular mass markers (shown in KDa); Mark 12 (Invitrogen).

10 **Figure 3 - Expression and purification of N[1-17]-LH_N/A fusion protein**

SDS-PAGE analysis of expression and purification of N[1-17]-LH_N/A from *E. coli*. In Figure 3, N[1-17]-LH_N/A is purified from *E. coli* BL21 cell paste using the methodology outlined in Example 9. Briefly, the soluble products obtained following cell disruption were applied to a nickel-charged affinity capture column. Bound proteins were eluted with 100 mM imidazole, treated with Factor Xa to activate the fusion protein and remove the maltose-binding protein (MBP) tag, then re-applied to a second nickel-charged affinity capture column. Samples from the purification procedure were assessed by SDS-PAGE (Panel A) and Western blotting (Panel B). Anti-nociceptin antisera (obtained from Abcam) were used as the primary antibody for Western blotting. The final purified material in the absence and presence of reducing agent is identified in the lanes marked [-] and [+] respectively.

25 **Figure 4 - Purification of a LC/A-nociceptin-H_N/A fusion protein**

Using the methodology outlined in Example 26, a LC/A-nociceptin-H_N/A fusion protein was purified from *E. coli* BL21 cells. Briefly, the soluble products obtained following cell disruption were applied to a nickel-charged affinity capture column. Bound proteins were eluted with 100 mM imidazole, treated with Factor Xa to activate the fusion protein and remove the maltose-binding protein (MBP) tag, then re-applied to a second nickel-charged affinity capture column. Samples from the purification procedure were assessed by SDS-PAGE (Panel A) and Western blotting

(Panel B). Anti-nociceptin antisera (obtained from Abcam) were used as the primary antibody for Western blotting. The final purified material in the absence and presence of reducing agent is identified in the lanes marked [-] and [+] respectively.

5 **Figure 5 - Purification of a nociceptin-LC/A-H_N/A fusion protein**

Using the methodology outlined in Example 26, a nociceptin-LC/A-H_N/A fusion protein was purified from *E. coli* BL21 cells. Briefly, the soluble products obtained following cell disruption were applied to a nickel-charged affinity capture column. Bound proteins were eluted with 100 mM imidazole, treated with Factor Xa to activate the fusion protein and remove the maltose-binding protein (MBP) tag, then re-applied to a second nickel-charged affinity capture column. Samples from the purification procedure were assessed by SDS-PAGE (Panel A) and Western blotting (Panel B). Anti-nociceptin antisera (obtained from Abcam) were used as the primary antibody for Western blotting. The final purified material in the absence and presence of reducing agent is identified in the lanes marked [-] and [+] respectively.

Figure 6 - Purification of a LC/C-nociceptin-H_N/C fusion protein

Using the methodology outlined in Example 26, an LC/C-nociceptin-H_N/C fusion protein was purified from *E. coli* BL21 cells. Briefly, the soluble products obtained following cell disruption were applied to a nickel-charged affinity capture column. Bound proteins were eluted with 100 mM imidazole, treated with Factor Xa to activate the fusion protein and remove the maltose-binding protein (MBP) tag, then re-applied to a second nickel-charged affinity capture column. Samples from the purification procedure were assessed by SDS-PAGE (Panel A) and Western blotting (Panel B). Anti-nociceptin antisera (obtained from Abcam) were used as the primary antibody for Western blotting. The final purified material in the absence and presence of reducing agent is identified in the lanes marked [-] and [+] respectively.

Figure 7 - Purification of a LC/A-met enkephalin-H_N/A fusion protein

Using the methodology outlined in Example 26, an LC/A-met enkephalin-H_N/A fusion
5 protein was purified from *E. coli* BL21 cells. Briefly, the soluble products obtained
following cell disruption were applied to a nickel-charged affinity capture column.
Bound proteins were eluted with 100 mM imidazole, treated with Factor Xa to
activate the fusion protein and remove the maltose-binding protein (MBP) tag, then
re-applied to a second nickel-charged affinity capture column. Samples from the
10 purification procedure were assessed by SDS-PAGE. The final purified material in
the absence and presence of reducing agent is identified in the lanes marked [-] and
[+] respectively.

**Figure 8 - Comparison of binding efficacy of a LC/A-nociceptin-H_N/A fusion
15 protein and a nociceptin-LC/A-H_N/A fusion protein**

The ability of nociceptin fusions to bind to the ORL₁ receptor was assessed using a
simple competition-based assay. Primary cultures of dorsal root ganglia (DRG) were
exposed to varying concentrations of test material in the presence of 1 nM [3H]-
20 nociceptin. The reduction in specific binding of the radiolabelled ligand was
assessed by scintillation counting, and plotted in comparison to the efficacy of
unlabelled ligand (Tocris nociceptin). It is clear that the LC/A-nociceptin-H_N/A fusion
is far superior to the nociceptin-LC/A-H_N/A fusion at interacting with the ORL₁
receptor.

25

Figure 9 - *In vitro* catalytic activity of a LC/A-nociceptin-H_N/A fusion protein

The *in vitro* endopeptidase activity of the purified LC/A-nociceptin-H_N/A fusion
protein was determined essentially as described in Chaddock *et al* 2002, Prot.
30 Express Purif. 25, 219-228. Briefly, SNAP-25 peptide immobilised to an ELISA plate
was exposed to varying concentrations of fusion protein for 1 hour at 37°C.

Following a series of washes, the amount of cleaved SNAP-25 peptide was quantified by reactivity with a specific antisera.

Figure 10 - Purification of a LC/A-nociceptin variant-H_N/A fusion protein

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Using the methodology outlined in Example 26, an LC/A-nociceptin variant-H_N/A fusion protein was purified from *E. coli* BL21 cells. Briefly, the soluble products obtained following cell disruption were applied to a nickel-charged affinity capture column. Bound proteins were eluted with 100 mM imidazole, treated with Factor Xa to activate the fusion protein and remove the maltose-binding protein (MBP) tag, then re-applied to a second nickel-charged affinity capture column. Samples from the purification procedure were assessed by SDS-PAGE. The final purified material in the absence and presence of reducing agent is identified in the lanes marked [-] and [+] respectively.

15

Figure 11 - Comparison of binding efficacy of a LC/A-nociceptin-H_N/A fusion protein and a LC/A-nociceptin variant-H_N/A fusion protein

The ability of nociceptin fusions to bind to the ORL₁ receptor was assessed using a simple competition-based assay. Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of test material in the presence of 1nM [3H]-nociceptin. The reduction in specific binding of the radiolabelled ligand was assessed by scintillation counting, and plotted in comparison to the efficacy of unlabelled ligand (Tocris nociceptin). It is clear that the LC/A-nociceptin variant-H_N/A fusion (CPNv-LHA) is superior to the LC/A-nociceptin variant-H_N/A fusion (CPN-LHA) at interacting with the ORL₁ receptor.

25

Figure 12 - Expressed / purified LC/A-nociceptin-H_N/A fusion protein family with variable spacer length product(s)

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Using the methodology outlined in Example 26, variants of the LC/A-CPN-H_N/A fusion-consisting of GS10, GS30 and HX27 are purified from *E. coli* cell paste.

Samples from the purification of LC/A-CPN(GS10)-H_N/A, LC/A-CPN(GS15)-H_N/A, LC/A-CPN(GS25)-H_N/A, LC/A-CPN(GS30)-H_N/A and LC/A-CPN(HX27)-H_N/A were assessed by SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPBE-A. Top panel: M = benchmark molecular mass markers; S = total *E. coli* protein soluble fraction; FT = proteins that did not bind to the Ni²⁺-charged Sepharose column; FUSION = fusion protein eluted by the addition of imidazole. Bottom panel: Lane 1 = benchmark molecular mass markers; Lane 2 = total *E. coli* protein soluble fraction; Lane 3 = purified material following initial capture on Ni²⁺-charged Sepharose; Lane 4 = Factor Xa treated material prior to final capture on Ni²⁺-charged Sepharose; Lane 5 = purified final material post activation with Factor Xa (5 µl); Lane 6 = purified final material post activation with Factor Xa (10 µl); Lane 7 = purified final material post activation with Factor Xa (20 µl); Lane 8 = purified final material post activation with Factor Xa + DTT (5 µl); Lane 9 = purified final material post activation with Factor Xa + DTT (10 µl); Lane 10 = purified final material post activation with Factor Xa + DTT (20 µl).

Figure 13 - Inhibition of SP release and cleavage of SNAP-25 by CPN-A

Briefly, primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPN-A for 24 hours. Cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of cleaved SNAP-25 was calculated by densitometric analysis and plotted against fusion concentration (dashed line). Material was also recovered for an analysis of substance P content using a specific EIA kit. Inhibition of substance P release is illustrated by the solid line. The fusion concentration required to achieve 50% maximal SNAP-25 cleavage is estimated to be 6.30±2.48 nM.

Figure 14 - Inhibition of SP release and cleavage of SNAP-25 over extended time periods after exposure of DRG to CPN-A

~~Primary cultures of dorsal root ganglia (DRG) were exposed to varying~~
5 concentrations of CPN-A for 24 hours. Botulinum neurotoxin (BoNT/A) was used as a control. After this initial exposure, extracellular material was removed by washing, and the cells incubated at 37°C for varying periods of time. At specific time points, cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of
10 cleaved SNAP-25 was calculated by densitometric analysis and illustrated by the dotted lines. Material was also recovered for an analysis of substance P content using a specific EIA kit. Inhibition of substance P release is illustrated by the solid lines.

15 **Figure 15 - Cleavage of SNAP-25 by CPNv-A**

Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPNv-A for 24 hours. Cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment
20 of SNAP-25 cleavage. The percentage of cleaved SNAP-25 was calculated by densitometric analysis. The fusion concentration required to achieve 50% maximal SNAP-25 cleavage is estimated to be 1.38 ± 0.36 nM.

25 **Figure 16 - Cleavage of SNAP-25 over extended time periods after exposure of DRG to CPNv-A**

Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPNv-A for 24 hours. CPN-A was used as a control. After this initial exposure, extracellular material was removed by washing, and the cells
30 incubated at 37°C for varying periods of time. At specific time points, cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of

cleaved SNAP-25 was calculated by densitometric analysis.

Figure 17 - CPNv-A fusion-mediated displacement of [3H]-nociceptin binding

5

The ability of nociceptin fusions to bind to the ORL₁ receptor was assessed using a simple competition-based assay. Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of test material in the presence of 1 nM [3H]-nociceptin. The reduction in specific binding of the radiolabelled ligand was assessed by scintillation counting, and plotted in comparison to the efficacy of unlabelled ligand (Tocris nociceptin). It is clear that the LC/A-nociceptin variant-H_N/A fusion (labelled as CPNv-LHnA) is superior to the LC/A-nociceptin-H_N/A fusion (labelled as CPN-LHnA) at interacting with the ORL₁ receptor.

Figure 18 - Expressed/purified CPNv(Ek)-A product

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPNv(Ek)-A. Lane 1 = benchmark molecular mass markers; Lane 2 = total *E. coli* protein soluble fraction; Lane 3 = purified material following initial capture on Ni²⁺-charged Sepharose; Lane 4 = purified final material post activation with enterokinase (5 µl); Lane 5 = purified final material post activation with enterokinase (10 µl); Lane 6 = purified final material post activation with enterokinase (20 µl); Lane 7 = purified final material post activation with enterokinase + DTT (5 µl); Lane 8 = purified final material post activation with enterokinase + DTT (10 µl); Lane 9 = purified final material post activation with enterokinase + DTT (20 µl).

30

Figure 19 - Cleavage of SNAP-25 by CPNv(Ek)-A

Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPNv(Ek)-A for 24 hours. Cellular proteins were separated by

SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of cleaved SNAP-25 was calculated by densitometric analysis. CPNv-A as prepared in Example 26 was used for comparison purposes. The percentage cleavage of SNAP-25 by CPNv(Ek)-A (labelled as En activated) and CPNv-A (labelled as Xa activated) are illustrated.

Figure 20 - Expressed / purified CPNv-C product

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPNv-C. Lane 1 = benchmark molecular mass markers; Lane 2 = total *E. coli* protein soluble fraction; Lane 3 = purified material following initial capture on Ni^{2+} -charged Sepharose; Lane 4 = Factor Xa treated material prior to final capture on Ni^{2+} -charged Sepharose; Lane 5 = purified material following second capture on Ni^{2+} -charged Sepharose; Lane 6 = final purified material; Lane 7 = final purified material + DTT; Lane 8 = benchmark molecular mass markers.

Figure 21 - Cleavage of syntaxin by CPNv-C

Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPNv-C for 24 hours. Cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-syntaxin to facilitate an assessment of syntaxin cleavage. The percentage of cleaved syntaxin was calculated by densitometric analysis. The fusion concentration required to achieve 50% maximal syntaxin cleavage is estimated to be 3.13 ± 1.96 nM.

Figure 22 - CPN-A efficacy in the Acute Capsaicin-Induced Mechanical Allodynia model

The ability of an LC/A-nociceptin- H_N /A fusion (CPN/A) to inhibit capsaicin-induced mechanical allodynia was evaluated following subcutaneous intraplantar injection in

the rat hind paw. Test animals were evaluated for paw withdrawal frequency (PWF%) in response to a 10 g Von Frey filament stimulus series (10 stimuli x 3 trials) prior to recruitment into the study (Pre-Treat); after subcutaneous intraplantar treatment with CPN/A but before capsaicin (Pre-CAP); and following capsaicin challenge post-injection of CPN/A (average of responses at 15' and 30'; CAP). Capsaicin challenge was achieved by injection of 10 μ L of a 0.3% solution. Sample dilutions were prepared in 0.5% BSA/saline.

Figure 23 - CPN-A efficacy in the Streptozotocin (STZ)-Induced Peripheral Diabetic Neuropathy (Neuropathic Pain) model

Male Sprague-Dawley rats (250-300 g) are treated with 65 mg/kg STZ in citrate buffer (I.V.) and blood glucose and lipid are measured weekly to define the readiness of the model. Paw Withdrawal Threshold (PWT) is measured in response to a Von Frey filament stimulus series over a period of time. Allodynia is said to be established when the PWT on two consecutive test dates (separated by 1 week) measures below 6 g on the scale. At this point, rats are randomized to either a saline group (negative efficacy control), gabapentin group (positive efficacy control) or a test group (CPN/A). Test materials (20-25 μ l) are injected subcutaneously as a single injection (except gabapentin) and the PWT is measured at 1 day post-treatment and periodically thereafter over a 2 week period. Gabapentin (30 mg/kg i.p. @ 3 ml/kg injection volume) is injected daily, 2 hours prior to the start of PWT testing.

Figure 24 - CPNv-A efficacy in the Acute Capsaicin-Induced Mechanical Allodynia model

The ability of an LC/A-nociceptin variant-H₁/A fusion (CPNv/A) to inhibit capsaicin-induced mechanical allodynia was evaluated following subcutaneous intraplantar injection in the rat hind paw. Test animals were evaluated for paw withdrawal frequency (PWF%) in response to a 10 g Von Frey filament stimulus series (10 stimuli x 3 trials) prior to recruitment into the study (Pre-Treat), after subcutaneous

intraplantar treatment with CPNv/A but before capsaicin (Pre-CAP), and following capsaicin challenge post-injection of CPNv/A (average of responses at 15' and 30'; CAP). Capsaicin challenge was achieved by injection of 10 μ L of a 0.3% solution. Sample dilutions were prepared in 0.5% BSA/saline. These data are expressed as a
5 normalized paw withdrawal frequency differential, in which the difference between the peak response (post-capsaicin) and the baseline response (pre-capsaicin) is expressed as a percentage. With this analysis, it can be seen that CPNv/A is more potent than CPN/A since a lower dose of CPNv/A is required to achieve similar analgesic effect to that seen with CPN/A.

10

Figure 25 - Expressed / purified LC/A-CPLE-H_N/A product

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species
15 of the expected molecular mass of CPLE-A. Lane 1 = benchmark molecular mass markers; Lane 2 = total *E. coli* protein soluble fraction; Lane 3 = purified material following initial capture on Ni²⁺-charged Sepharose; Lane 4 = Factor Xa treated material prior to final capture on Ni²⁺-charged Sepharose; Lane 5 = purified material following second capture on Ni²⁺-charged Sepharose; Lane 6 = final purified
20 material; Lane 7 = final purified material + DTT.

Figure 26 - Expressed / purified LC/A-CPBE-H_N/A product

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The
25 electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPBE-A. Lane 1 = total *E. coli* protein soluble fraction; Lane 2 = purified material following initial capture on Ni²⁺-charged Sepharose; Lane 3 = Factor Xa treated material prior to final capture on Ni²⁺-charged Sepharose; Lane 4 = purified final material post activation with Factor Xa (5 μ l); Lane 5 = purified final material post activation with Factor Xa (10 μ l); Lane 6 =
30 purified final material post activation with Factor Xa (20 μ l); Lane 7 = purified final material post activation with Factor Xa + DTT (5 μ l); Lane 8 = purified final material

post activation with Factor Xa + DTT (10 μ l); Lane 9 = purified final material post activation with Factor Xa + DTT (20 μ l); Lane 10 = benchmark molecular mass markers.

5 **Figure 27 - Expressed / purified CPOP-A product**

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPOP-A. Lane 1 = benchmark molecular mass
10 markers; Lane 2 = purified material following initial capture on Ni^{2+} -charged Sepharose; Lane 3 = Factor Xa treated material prior to final capture on Ni^{2+} -charged Sepharose; Lane 4 = purified material following second capture on Ni^{2+} -charged Sepharose; Lane 5 = purified final material post activation with Factor Xa (5 μ l); Lane 6 = purified final material post activation with Factor Xa (10 μ l); Lane 7 =
15 purified final material post activation with Factor Xa (20 μ l); Lane 8 = purified final material post activation with Factor Xa + DTT (5 μ l); Lane 9 = purified final material post activation with Factor Xa + DTT (10 μ l); Lane 10 = purified final material post activation with Factor Xa + DTT (20 μ l).

20 **Figure 28 - Expressed / purified CPOPv-A product**

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPOPv-A. Lane 1 = benchmark molecular mass
25 markers; Lane 2 = total *E. coli* protein soluble fraction; Lane 3 = purified material following initial capture on Ni^{2+} -charged Sepharose; Lane 4 = Factor Xa treated material prior to final capture on Ni^{2+} -charged Sepharose; Lane 5 = purified final material post activation with Factor Xa (5 μ l); Lane 6 = purified final material post activation with Factor Xa (10 μ l); Lane 7 = purified final material post activation with
30 Factor Xa (20 μ l); Lane 8 = purified final material post activation with Factor Xa + DTT (5 μ l); Lane 9 = purified final material post activation with Factor Xa + DTT (10 μ l); Lane 10 = purified final material post activation with Factor Xa + DTT (20 μ l).

Figure 29 - *In vitro* SNAP-25 cleavage in a DRG cell model

5 Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPOPv-A for 24 hours. Cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of cleaved SNAP-25 was calculated by densitometric analysis.

10

Figure 30 - Expressed / purified CPNv-A-FXa-HT (removable his-tag)

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species
15 of the expected molecular mass of CPNv-A-FXa-HT. Lane 1 = benchmark molecular mass markers; Lane 2 = total *E. coli* protein soluble fraction; Lane 3 = Factor Xa treated material prior to final capture on Ni²⁺-charged Sepharose; Lane 4 = purified final material post activation with Factor Xa; Lane 5 = purified final material post activation with Factor Xa + DTT.

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Figure 31 - *In vitro* efficacy of LC/A-nociceptin-H_N/A fusion proteins with variable spacer length, as assessed by ligand competition assay

The ability of LC/A-nociceptin-H_N/A fusions of variable spacer length to bind to the
25 ORL₁ receptor was assessed using a simple competition-based assay. Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of test material in the presence of 1 nM [3H]-nociceptin. The reduction in specific binding of the radiolabelled ligand was assessed by scintillation counting, and plotted in comparison to the efficacy of unlabelled ligand (Tocris nociceptin). The upper panel
30 illustrates the displacement characteristics of the GS0, GS20, GS30 and Hx27 spacers, whilst the lower panel illustrates the displacement achieved by the GS10, GS15 and GS25 spaced fusion proteins. It is concluded that the GS0 and GS30

spacers are ineffective, and the GS10 is poorly effective, at displacing nociceptin from the ORL1 receptor.

Figure 32 - *In vitro* efficacy of LC/A-nociceptin-H_N/A fusion proteins with variable spacer length, as assessed by *in vitro* SNAP-25 cleavage

Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPN-A (of variable spacer length) for 24 hours. Cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of cleaved SNAP-25 was calculated by densitometric analysis. The poorly effective binding characteristics of the GS10 spaced fusion protein (see Figure 28) are reflected in the higher concentrations of fusion required to achieve cleavage of intracellular SNAP-25. GS0 and GS30 spaced fusion proteins were completely ineffective (data not shown). GS15, 20 and 25-spaced fusion proteins were similarly effective.

SEQ ID Nos

SEQ ID1	DNA sequence of N[1-17]
20 SEQ ID2	Protein Sequence of N[1-17]
SEQ ID3	DNA sequence of N[1-11]
SEQ ID4	Protein sequence of N[1-11]
SEQ ID5	DNA sequence of N[[Y10]1-11]
SEQ ID6	Protein sequence of N[[Y10]1-11]
25 SEQ ID7	DNA sequence of N[[Y11]1-11]
SEQ ID8	Protein sequence of N[[Y11]1-11]
SEQ ID9	DNA sequence of N[[Y14]1-17]
SEQ ID10	Protein sequence of N[[Y14]1-17]
SEQ ID11	DNA sequence of N[1-13]
30 SEQ ID12	Protein sequence of N[1-13]
SEQ ID13	DNA sequence of Nv (also known as N[[R14K15]1-17])
SEQ ID14	Protein sequence of Nv (also known as N[[R14K15]1-17])

	SEQ ID15	DNA sequence of N[1-17]-LH _N /A fusion protein
	SEQ ID16	Protein sequence of N[1-17]-LH _N /A fusion protein
	SEQ ID17	DNA sequence of N[[Y11]1-11]-LHN/A fusion protein
	SEQ ID18	Protein sequence of N[[Y11]1-11]-LHN/A fusion protein
5	SEQ ID19	DNA sequence of N[1-13]-LHN/A fusion protein
	SEQ ID20	Protein sequence of N[1-13]-LHN/A fusion protein
	SEQ ID21	DNA sequence of LHN/A-N[1-17] fusion protein
	SEQ ID22	Protein sequence of LHN/A-N[1-17] fusion protein
	SEQ ID23	DNA sequence of LHN/C-N[1-11] fusion protein
10	SEQ ID24	Protein sequence of LHN/C-N[1-11] fusion protein
	SEQ ID25	DNA sequence of N[[Y14]1-17]-LHN/C fusion protein
	SEQ ID26	Protein sequence of N[[Y14]1-17]-LHN/C fusion protein
	SEQ ID27	DNA sequence of the LC/A
	SEQ ID28	DNA sequence of the H _N /A
15	SEQ ID29	DNA sequence of the LC/B
	SEQ ID30	DNA sequence of the H _N /B
	SEQ ID31	DNA sequence of the LC/C
	SEQ ID32	DNA sequence of the H _N /C
	SEQ ID33	DNA sequence of the CPN-A linker
20	SEQ ID34	DNA sequence of the A linker
	SEQ ID35	DNA sequence of the N-terminal presentation nociceptin insert
	SEQ ID36	DNA sequence of the CPN-C linker
	SEQ ID37	DNA sequence of the CPBE-A linker
	SEQ ID38	DNA sequence of the CPNvar-A linker
25	SEQ ID39	DNA sequence of the LC/A-CPN-H _N /A fusion
	SEQ ID40	Protein sequence of the LC/A-CPN-H _N /A fusion
	SEQ ID41	DNA sequence of the N-LC/A-H _N /A fusion
	SEQ ID42	Protein sequence of the N-LC/A-H _N /A fusion
	SEQ ID43	DNA sequence of the LC/C-CPN-H _N /C fusion
30	SEQ ID44	Protein sequence of the LC/C-CPN-H _N /C fusion
	SEQ ID45	DNA sequence of the LC/C-CPN-H _N /C (A-linker) fusion
	SEQ ID46	Protein sequence of the LC/C-CPN-H _N /C (A-linker) fusion

- SEQ ID47 DNA sequence of the LC/A-CPME-H_N/A fusion
- SEQ ID48 Protein sequence of the LC/A-CPME-H_N/A fusion
- SEQ ID49 DNA sequence of the LC/A-CPBE-H_N/A fusion
- ~~SEQ ID50 Protein sequence of the LC/A-CPBE-H_N/A fusion~~
- 5 SEQ ID51 DNA sequence of the LC/A-CPNv-H_N/A fusion
- SEQ ID52 Protein sequence of the LC/A-CPNv-H_N/A fusion
- SEQ ID53 DNA sequence of the LC/A-CPN[1-11]-HN/A fusion
- SEQ ID54 Protein sequence of the LC/A-CPN[1-11]-HN/A fusion
- SEQ ID55 DNA sequence of the LC/A-CPN[[Y10]1-11]-HN/A fusion
- 10 SEQ ID56 Protein sequence of the LC/A-CPN[[Y10]1-11]-HN/A fusion
- SEQ ID57 DNA sequence of the LC/A-CPN[[Y11]1-11]-HN/A fusion
- SEQ ID58 Protein sequence of the LC/A-CPN[[Y11]1-11]-HN/A fusion
- SEQ ID59 DNA sequence of the LC/A-CPN[[Y14]1-17]-HN/A fusion
- SEQ ID60 Protein sequence of the LC/A-CPN[[Y14]1-17]-HN/A fusion
- 15 SEQ ID61 DNA sequence of the LC/A-CPN[1-13]-HN/A fusion
- SEQ ID62 Protein sequence of the LC/A-CPN[1-13]-HN/A fusion
- SEQ ID63 DNA sequence of the nociceptin-spacer-LC/A-H_N/A fusion
- SEQ ID64 Protein sequence of the nociceptin-spacer-LC/A-H_N/A fusion
- SEQ ID65 DNA sequence of the CPN-A GS10 linker
- 20 SEQ ID66 DNA sequence of the CPN-A GS15 linker
- SEQ ID67 DNA sequence of the CPN-A GS25 linker
- SEQ ID68 DNA sequence of the CPN-A GS30 linker
- SEQ ID69 DNA sequence of the CPN-A HX27 linker
- SEQ ID70 DNA sequence of the LC/A-CPN(GS15)-H_N/A fusion
- 25 SEQ ID71 Protein sequence of the LC/A-CPN(GS15)-H_N/A fusion
- SEQ ID72 DNA sequence of the LC/A-CPN(GS25)-H_N/A fusion
- SEQ ID73 Protein sequence of the LC/A-CPN(GS25)-H_N/A fusion
- SEQ ID74 DNA sequence of the CPNvar-A Enterokinase activatable linker
- SEQ ID75 DNA sequence of the LC/A-CPNv(Ek)-H_N/A fusion
- 30 SEQ ID76 Protein sequence of the LC/A-CPNv(Ek)-H_N/A fusion
- SEQ ID77 DNA sequence of the CPNvar-A linker
- ~~SEQ ID78 DNA sequence of the LC/C-CPNv-H_N/C fusion (act. A)~~

- SEQ ID79 Protein sequence of the LC/C-CPNv-H_N/C fusion (act. A)
- SEQ ID80 DNA sequence of the LC/A-CPLE-H_N/A fusion
- SEQ ID81 Protein sequence of the LC/A-CPLE-H_N/A fusion
- SEQ ID82 DNA sequence of the LC/A-CPOP-H_N/A fusion
- 5 SEQ ID83 Protein sequence of the LC/A-CPOP-H_N/A fusion
- SEQ ID84 DNA sequence of the LC/A-CPOPv-H_N/A fusion
- SEQ ID85 Protein sequence of the LC/A-CPOPv-H_N/A fusion
- SEQ ID86 DNA sequence of the IgA protease
- SEQ ID87 DNA sequence of the IgA-CPNv-H_N/A fusion
- 10 SEQ ID88 Protein sequence of the IgA-CPNv-H_N/A fusion
- SEQ ID89 DNA sequence of the FXa-HT
- SEQ ID90 DNA sequence of the CPNv-A-FXa-HT
- SEQ ID91 Protein sequence of the CPNv-A-FXa-HT fusion
- SEQ ID92 DNA sequence of the DT translocation domain
- 15 SEQ ID93 DNA sequence of the CPLE-DT-A
- SEQ ID94 Protein sequence of the CPLE-DT-A fusion
- SEQ ID95 DNA sequence of the TeNT LC
- SEQ ID96 DNA sequence of the CPNv-TENT LC
- SEQ ID97 Protein sequence of the CPNV-TeNT LC fusion
- 20 SEQ ID98 DNA sequence of the CPNvar-C linker
- SEQ ID99 DNA sequence of the LC/C-CPNv-H_N/C fusion (act. C)
- SEQ ID100 Protein sequence of the LC/C-CPNv-H_N/C fusion (act. C)

25 **Examples**

Example 1 – Confirmation of TM Agonist Activity by measuring release of substance P from neuronal cell cultures

30 ***Materials***

Substance P EIA is obtained from R&D Systems, UK.

Methods

Primary neuronal cultures of eDRG are established as described previously (Duggan *et al.*, 2002). Substance P release from the cultures is assessed by EIA, essentially as described previously (Duggan *et al.*, 2002). The TM of interest is added to the neuronal cultures (established for at least 2 weeks prior to treatment); control cultures are performed in parallel by addition of vehicle in place of TM. Stimulated (100 mM KCl) and basal release, together with total cell lysate content, of substance P are obtained for both control and TM treated cultures. Substance P immunoreactivity is measured using Substance P Enzyme Immunoassay Kits (Cayman Chemical Company, USA or R&D Systems, UK) according to manufacturers' instructions.

The amount of Substance P released by the neuronal cells in the presence of the TM of interest is compared to the release obtained in the presence and absence of 100 mM KCl. Stimulation of Substance P release by the TM of interest above the basal release, establishes that the TM of interest is an "agonist ligand" as defined in this specification. If desired the stimulation of Substance P release by the TM of interest can be compared to a standard Substance P release-curve produced using the natural ORL-1 receptor ligand, nociceptin (Tocris).

Example 2 - Expression and purification of catalytically active LH_N/A

Materials

Synthetic DNA obtained from Sigma Genosys.
Restriction enzymes obtained from New England Biolabs.

Methods

The expression and purification of catalytically active LH_N/A was carried out essentially as described in Sutton *et al.*, (2005), Prot. Express. Purif., 40, pp 31-41.

Briefly, DNA encoding the light chain plus 423 amino acids from the N-terminal of the heavy chain of BoNT/A was synthesised by Sigma-Genosys to produce a synthetic

LH_N/A gene with an *E. coli* codon bias. The linker region between the light chain and H_N domain was engineered to contain a Factor Xa cleavage site by splice-overlap extension PCR. Two PCR products were generated using primer pairs consisting of a long, mutagenic primer and a shorter, non-mutagenic primer:

5

(5'-tccaaaactaaatctctgATAGAAGGTAGAAacaaagcgctgaacgac) with
(5'-CTTGATGTACTCTGTGAACGTGCTC); and

10

(5'-gtcggtcagcgcttggTCTACCTTCTATcagagatttagtttggga) with
(5'-ATGGAGTTCGTTAACAAACAGTTC).

The products from these two reactions were used as templates for the splice-overlap extension PCR. A further PCR reaction was set up to add *Bam*HI and *Sa*II sites at either end of the activatable recLH_N/A gene and these sites were used for insertion
15 into an Invitrogen gateway entry vector. The entry vector was then used, along with a gateway recombination site adapted pMAL c2x, in a LR clonase reaction to form pMAL c2x recLH_N/A. The pMAL c2x recLH_N/A was modified to incorporate a 6^{*}HIS tag at the N-terminus of the MBP. This was achieved by the insertion of annealed oligonucleotides encoding the HIS tag into the *Nde*I site of pMAL.

20

The expression vector expressing LH_N/A was transformed into *E. coli* HMS174 or AD494(DE3) (Novagen). Cultures were grown in Terrific broth complex medium supplemented with ZnCl₂ (1 μM), ampicillin (100 μg/ml), 0.2% (w/v) glucose. Parameters for expression of all the constructs were initially determined in shake
25 flask cultures before transferring into 8 L fermentor systems. Starter cultures were grown for 16 hours at 37°C, 220 rpm and used to inoculate 1 L in which growth was continued at 37°C, 250 rpm. At an OD_{600 nm} of 0.6 the temperature was reduced to 25°C for 30 minutes before induction with 1 mM IPTG. Induction was continued for 4 hours before the cells were harvested and stored at -70°C.

30

Typically 16 g of cell paste was suspended in 160 ml PBS and lysed by sonication (MSE Soniprep 150). The resulting lysate was clarified by centrifugation prior

loading onto a 25 ml amylose column and eluted with 10 mM maltose in PBS. The eluant contained approx. 50% pure fusion protein and was treated with Factor Xa (1 unit Factor Xa /100 µg fusion protein; 20 hours; 26°C) to remove the HISMBP and cleave the LG-H_N junction to activate the protein. After incubation the sample was
5 filtered (0.45 µm) and diluted two fold with water to give a 0.5 x PBS buffer composition. The cleaved, filtered and diluted recLH_N/A was processed through a Q Sepharose FF column (10 ml) and eluted with a step gradient of 80 mM NaCl containing HISMBP and 120 mM NaCl containing approx. 75% pure recLH_N/A. The addition of His tag to MBP overcame previous co-elution problems with LH_N/A and
10 MBP. As a final polishing step to ensure complete removal of the HISMBP, the 120 mM NaCl elution from the Q Sepharose column was passed through a Nickel charged 5 ml HisTrap column (Amersham). The flow through from the HisTrap column contained approx. 95% pure recLH_N/A (see the Figures in Sutton *et al.*, (2005), Prot. Express. Purif., 40, pp 31-41 for an illustration of the purification
15 scheme for LH_N/A).

Example 3 - Expression and purification of catalytically active recombinant LH_N/B

20 The methodology described below will purify catalytically active LH_N/B protease from *E. coli* transformed with the appropriate plasmid encoding the LH_N/B polypeptide. It should be noted that various sequences of suitable LH_N/B polypeptides have been described in PCT/GB97/02273, granted US 6 461617 and US patent application 10/241596, incorporated herein by reference.

25

Methods

The coding region for LH_N/B is inserted in-frame to the 3' of the gene encoding maltose binding protein (MBP) in the expression vector pMAL (New England Biolabs) to create pMAL- c2x-LH_N/B. In this construct, the expressed MBP and LH_N/B polypeptides are separated by a Factor Xa cleavage site, and the LC and H_N domains are separated by a peptide that is susceptible to cleavage with enterokinase. The expression clone is termed pMAL-c2X-synLH_N/B.

pMAL-c2X-synLH_N/B is transformed into *E. coli* HMS174 and cultured in Terrific broth complex medium in 8 L fermentor systems. Pre-induction bacterial growth is maintained at 37°C to an OD_{600 nm} of 5.0, at which stage expression of recMBP-LH_N/B is induced by addition of IPTG to 0.5 mM and a reduction in temperature to 30°C. After four hours at 30°C the bacteria are harvested by centrifugation and the resulting paste stored at -70°C.

The cell paste is resuspended in 20 mM Hepes pH 7.2, 125 mM NaCl, 1 µM ZnCl₂ and cell disruption achieved using an APV-Gaulin lab model 1000 homogeniser or a MSE Soniprep 150 sonicator. The resulting suspension is clarified by centrifugation prior to purification.

Following cell disruption, the MBP-fusion protein is captured either on an amylose affinity resin in 20 mM Hepes pH 7.2, 125 mM NaCl, 1 µM ZnCl₂, or on a Q-Sepharose FF anion-exchange resin in 50 mM Hepes pH 7.2, 1 µM ZnCl₂ with no salt. A single peak is eluted from the amylose resin in the same buffer plus 10 mM maltose and from the Q-Sepharose in 150-200 mM salt. Cleavage of the MBP-LH_N/B junction is completed in an 18 hours incubation step at 22°C with Factor Xa (NEB) at 1 U/50 µg fusion protein. A substrate (MBP-LH_N/B) concentration of at least 4 mg/ml is desirable for efficient cleavage to take place.

The cleaved protein is diluted with 20 mM Hepes to a buffer composition of 20 mM Hepes, 25 mM NaCl, 1 µM ZnCl₂, pH 7.2 and processed through a Q Sepharose column to separate the MBP from LH_N/B. The LH_N/B is eluted from the Q-Sepharose column with 120-170 mM salt. The linker between the light chain and H_N domain is then nicked by incubation with enterokinase at 1 U/100 µg of LH_N/B at 22°C for 16 hours. Finally, the enterokinase is separated from the nicked LH_N/B and other contaminating proteins on a Benzamidine Sepharose column, the enzyme preferentially binding to the resin over an incubation of 30 minutes at 4°C. Purified LH_N/B is stored at -20°C until required. See Figure 1 for an illustration of the purification scheme for recLH_N/B.

Example 4 - Expression and purification of catalytically active recombinant LH_N/C

The coding region for LH_N/C is inserted in-frame to the 3' of the gene encoding maltose binding protein (MBP) in the expression vector pMAL (New England Biolabs) to create pMAL- c2x-LH_N/C. In this construct the expressed MBP and LH_N/C polypeptides are separated by a Factor Xa cleavage site.

pMAL-c2x-LH_N/C is transformed into *E. coli* AD494 (DE3, IRL) and cultured in Terrific broth complex medium in 8 L fermentor systems. Pre-induction bacterial growth are maintained at 30°C to an OD_{600 nm} of 8.0, at which stage expression of recMBP-c2x-LH_N/C is induced by addition of IPTG to 0.5 mM and a reduction in temperature of culture to 25°C. After 4 hours at 25°C the bacteria are harvested by centrifugation and the resulting paste stored at -70°C.

The cell paste is resuspended in 50 mM Hepes pH 7.2, 1 µM ZnCl₂ at 1:6 (w/v) and cell disruption is achieved using an APV-Gaulin lab model 1000 homogeniser or a MSE Soniprep 150 sonicator. The resulting suspension is clarified by centrifugation prior to purification.

5

Following cell disruption and clarification, the MBP-fusion protein is separated on a Q-Sepharose Fast Flow anion-exchange resin in 50 mM Hepes pH 7.2, 1 µM ZnCl₂ and eluted with the same buffer plus 100 mM NaCl. A double point cleavage is performed at the MBP-LH_N/C junction and the H_N-LC linker in a single incubation step with Factor Xa. The reaction is completed in a 16-hour incubation step at 22°C with Factor Xa (NEB) at 1 U/100 lg fusion protein. The cleaved protein is diluted with 20 mM Hepes to a buffer composition of 20 mM Hepes, 25 mM NaCl, pH 7.2 and processed through a second Q-Sepharose column to separate the MBP from LH_N/C. Activated (disulphide-bonded cleaved linker) LH_N/C is eluted from the Q-Sepharose column by a salt gradient (20 mM Hepes, 500 mM NaCl, 1 µM ZnCl₂, pH 7.2) in 120-170 mM salt. See Figure 2 for an illustration of the purification of

15

LH_N/C.

Example 5 - Production of a chemical conjugate of nociceptin and LH_N/A

5 *Materials*

C-terminally extended nociceptin peptide obtained from Sigma Genosys.
Conjugation chemicals obtained from Pierce.

Methods

- 10 In order to couple the nociceptin peptide via a C-terminal Cys, the peptide was first synthesised (by standard procedures, commercially obtainable) to include a Cys as the final C-terminal amino acid.

This peptide was then used as the second component in a sulphydryl based
15 coupling reaction as described below (see also previous publications WO 99/17806 and WO 96/33273 and Duggan *et al.*, (2002), J. Biol. Chem. 277, 24846-34852 and Chaddock *et al.*, (2000), Infect Immun., 68, 2587-2593).

Sulphydryl based coupling reaction

- 20 Briefly, approximately two reactive leaving groups were introduced into LH_N/A (5 mg/ml in phosphate-buffered saline) by reaction with *N*-succinimidyl-3-(2-pyridyldithio)propionate (SPDP).

Derivatised material was isolated from excess SPDP by size exclusion
25 chromatography. Reconstituted cysteine-tagged nociceptin ligand was mixed with the derivatised LH_N/A in a 4:1 molar ratio, and incubated at room temperature for 1 hour with gentle agitation in order to create a chemical conjugate through a reducible covalent disulphide bond. Initial fractionation of the conjugate mixture to remove unconjugated peptide was performed by size exclusion chromatography
30 (Superose-12, or Superdex G-200 depending on scale of conjugation).

Example 6 - Production of a chemical conjugate of nociceptin and LH_N/B

Materials

- 5 C-terminally extended nociceptin peptide obtained from Sigma Genosys.
Conjugation chemicals obtained from Pierce.

Methods

- Lyophilised nociceptin was dissolved by the addition of water and dialysed into MES
10 buffer (0.1 M MES, 0.1 M NaCl, pH 5.0). To this solution (at a concentration of about
0.3 mg/ml) was added PDPH (100 mg/ml in DMF) to a final concentration of
1 mg/ml. After mixing, solid EDAC was added to produce a final concentration of
about 0.2 mg/ml. The reaction was allowed to proceed for at least 30 minutes at
room temperature. Excess PDPH was then removed by desalting over a PD-10
15 column (Pharmacia) previously equilibrated with MES buffer.

- An amount of LH_N/B equivalent to half the weight of nociceptin used dissolved in
triethanolamine buffer (0.02 M triethanolamine/HCl, 0.1 M sodium chloride, pH 7.8)
at a concentration of about 1 mg/ml, was reacted with Traut's reagent (100 mM stock
20 solution in 1 M triethanolamine/HCl, pH 8.0) at a final concentration of 2 mM. After
1 hour, the LH_N/B was desalted into PBSE (phosphate buffered saline with 1 mM
EDTA) using a PD-10 column (Pharmacia). The protein peak from the column
eluate was concentrated using a Microcon 50 (Amicon) to a concentration of about
2 mg/ml.

- 25 The derivatised nociceptin was subjected to a final concentration step resulting in a
reduction in volume to less than 10% of the starting volume and then mixed with the
derivatised LH_N/B overnight at room temperature. The products of the reaction were
analysed by polyacrylamide gel electrophoresis in the presence of sodium dodecyl-
sulphate (SDS-PAGE).
30

The conjugate resulting from the above reaction was partially purified by size

exclusion chromatography over Bio-Gel P-100 (BioRad). The elution profile was followed by measuring the optical density at 280 nm and SDS-PAGE analysis of the fractions. This allowed the separation of conjugate from free nociceptin and by-products of the reaction.

5

Example 7 - Production of a chemical conjugate of nociceptin 1-11 and LH_N/B

Materials

C-terminally extended nociceptin 1-11 peptide obtained from Sigma Genosys.

10 Conjugation chemicals obtained from Pierce.

Methods

In order to couple the nociceptin 1-11 peptide via a C-terminal Cys, the peptide was first synthesised (by standard procedures, commercially obtainable) to include a

15 Cys as the final C-terminal amino acid.

This peptide was then used as the second component in a sulphydryl based coupling reaction as described in Example 5.

20 Example 8 - Production of a chemical conjugate of nociceptin N[[Y14]1-17] and LH_N/C

Materials

C-terminally extended nociceptin N[[Y14]1-17] peptide obtained from Sigma

25 Genosys.

Conjugation chemicals obtained from Pierce.

Methods

In order to couple the peptide via a C-terminal Cys, the peptide was first synthesised (by standard procedures, commercially obtainable) to include a Cys as the final C-terminal amino acid.

30

This peptide was then used as the second component in a sulphydryl based coupling reaction as described in Example 5.

**Example 9 - Recombinant production of a single polypeptide fusion of
5 nociceptin-LH_N/A (SEQ ID15 and SEQ ID16)**

The DNA sequence for the nociceptin-LH_N/A was designed by back translation of the LC/A, H_N/A, and nociceptin amino acid sequences. The complete ORF containing the nociceptin-LC/A-activation loop-H_N/A sequence was assembled within standard
10 DNA sequence manipulation software (EditSeq). The activation loop between the LC/A cysteine and the H_N/A cysteine (CVRGIITSKTKSLDKGYNKALNDLC) was modified to incorporate a Factor Xa protease recognition site.

Restriction sites appropriate to facilitate cloning into the required expression vector
15 (for example BamHI/Sall) were incorporated at the 5' and 3' ends respectively of the sequence maintaining the correct reading frame. The DNA sequence was screened (using software such as MapDraw, DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any cleavage sequences that were found to be common to those required by the cloning system were removed
20 manually from the proposed coding sequence ensuring common *E. coli* codon usage was maintained. *E. coli* codon usage was assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, 13 September 2004).

25

This optimised DNA sequence containing the nociceptin-LC/A-activation loop-H_N/A open reading frame (ORF) was then commercially synthesized and provided in the pCR 4 vector.

30 The DNA encoding the nociceptin-LH_N/A fusion was isolated from pCR 4 and transferred into pMAL vector backbone to facilitate protein expression. The resultant pMAL NO-LHN/A vector was transformed into competent *E. coli* BL21 and correct

transformants selected. A single colony of pMAL NO-LH_N/A was grown in Terrific broth complex medium supplemented with ZnCl₂ (1 mM), ampicillin (100 µg/ml), 0.2% (w/v) glucose. Expression of the insert was induced by the addition of IPTG (0.1 mM) and the culture maintained at 16°C for 16 hours. After this period of
5 expression the bacteria were isolated by centrifugation and the cell pellet stored at -20°C until use.

10 g of *E. coli* BL21 cell paste was defrosted in a falcon tube containing 25 ml 50 mM HEPES, pH 7.2, 200 mM NaCl. The thawed cell paste was made up to 80 ml
10 with 50 mM HEPES, pH 7.2, 200 mM NaCl and sonicated on ice 30 seconds on, 30 seconds off for 10 cycles at a power of 22 microns ensuring the sample remained cool. The lysed cells were centrifuged at 18 000 rpm, 4°C for 30 minutes. The supernatant was loaded onto a 0.1 M NiSO₄ charged chelating column (20-30 ml column is sufficient) and equilibrated with 50 mM HEPES, pH 7.2, 200 mM NaCl.

15 Using a step gradient of 10 and 40 mM imidazol, the non-specific bound protein was washed away and the fusion protein eluted with 100 mM imidazol. The eluted fusion protein was dialysed against 5 L of 50 mM HEPES, pH 7.2, 200 mM NaCl at 4°C overnight and the OD of the dialysed fusion protein measured. 1 unit of Factor Xa
20 was added per 100 µg fusion protein and incubated at 25°C static overnight. The cleavage mixture was loaded onto a 0.1 M NiSO₄ charged Chelating column (20-30 ml column is sufficient) and equilibrated with 50 mM HEPES, pH 7.2, 200 mM NaCl.

25 Using a step gradient of 10 and 40 mM imidazol, the non-specific bound protein was washed away and the fusion protein eluted with 100 mM imidazol. The eluted fusion protein was dialysed against 5 L of 50 mM HEPES, pH 7.2, 200 mM NaCl at 4°C overnight and the fusion concentrated to about 2 mg/ml, aliquoted and stored at -20°C.

30

Figure 3 shows the SDS-PAGE analysis of expression and purification of N[1-17]-

LH_N/A

Example 10 – Recombinant production of a single polypeptide fusion of (nociceptin 1-11)-LH_N/B

5 The DNA sequence for the (nociceptin 1-11)-LH_N/B was designed by back translation of the LC/B, H_N/B, and nociceptin 1-11 amino acid sequences. The complete ORF containing the (nociceptin1-11)-LC/B-activation loop-H_N/B sequence was assembled within standard DNA sequence manipulation software (EditSeq). The activation loop between the LC/B cysteine and the H_N/B cysteine was modified
10 to incorporate a Factor Xa protease recognition site.

The recombinant fusion protein was then produced essentially as described in Example 9.

15 **Example 11 – Recombinant production of a single polypeptide fusion of (nociceptin N[[Y14]1-17]) - LH_N/C (SEQ ID25 and SEQ ID26)**

The DNA sequence for the nociceptin N[[Y14]1-17] was designed by back translation of the LC/C, H_N/C, and nociceptin N[[Y14]1-17] amino acid sequences. The
20 complete ORF containing the (nociceptin N[[Y14]1-17])-LC/C-activation loop-H_N/C sequence was assembled within standard DNA sequence manipulation software (EditSeq). The activation loop between the LC/C cysteine and the H_N/C cysteine was modified to incorporate a Factor Xa protease recognition site.

25 The recombinant fusion protein was then produced essentially as described in Example 9.

30 **Example 12 – Recombinant production of a single polypeptide fusion of LH_N/C-(nociceptin 1-11) (SEQ ID23 and SEQ ID24)**

The DNA sequence for the LH_N/C-(nociceptin 1-11) was designed by back

translation of the LC/C, H_N/C and nociceptin 1-11 amino acid sequences. The complete ORF (SEQ ID23) containing the LC/C-activation loop-H_N/C-flexible spacer-(nociceptin 1-11) was assembled within standard DNA sequence manipulation software (EditSeq).-

5

The recombinant fusion protein (SEQ ID24) was then produced essentially as described in Example 9.

Example 13 - Production of a conjugate for delivery of DNA encoding LC/C into a cell

10

The construction of a nociceptin-H_N-[LC/C] conjugate is described below, where [LC/C] represents the polylysine condensed DNA encoding the light chain of botulinum neurotoxin type C.

15

Materials

SPDP is from Pierce Chemical Co.

Additional reagents are obtained from Sigma Ltd.

Methods

20

Using a plasmid containing the gene encoding LC/C under the control of a CMV (immediate early) promoter, condensation of DNA was achieved using SPDP-derivatised polylysine to a ratio of 2 DNA to 1 polylysine. Conjugates were then prepared by mixing condensed DNA (0.4 mg/ml) with H_N-nociceptin (100 µg/ml) for 16 h at 25°C. The SPDP-derivatised polylysine and the free -SH group present on the H_N domain combine to facilitate covalent attachment of the DNA and protein.

25

Example 14 - Production of a conjugate for delivery of DNA encoding LC/B into a cell

30

The construction of a (nociceptin 1-11)-H_N-[LC/B] conjugate is described below, where [LC/B] represents the polylysine condensed DNA encoding the light chain of

botulinum neurotoxin type B.

Materials

SPDP is from Pierce Chemical Co.

5 Additional reagents are obtained from Sigma Ltd.

Methods

Using a plasmid containing the gene encoding LC/B under the control of a CMV (immediate early) promoter, condensation of DNA was achieved using SPDP-
10 derivatised polylysine to a ratio of 2 DNA to 1 polylysine. Conjugates were then prepared by mixing condensed DNA (0.4 mg/ml) with H_N-(nociceptin 1-11) (100 µg/ml) for 16 h at 25°C. The SPDP-derivatised polylysine and the free -SH group present on the H_N domain combine to facilitate covalent attachment of the DNA and protein.

15 —

Example 15 – Assessment of the activity of nociceptin-LH_N/A in substance P releasing neuronal cells

Using methodology described in Duggan *et al.*, (2002, J. Biol. Chem., 277, 34846-
20 34852), the activity of nociceptin-LH_N/A in substance P releasing neuronal cells was assessed.

Nociceptin-LH_N/A fusion protein was applied to 2-week old dorsal root ganglia neuronal cultures, and incubated at 37°C for 16 hours. Following the incubation, the
25 media was removed and the ability of the cells to undergo stimulated release of substance P (SP) was assessed.

The release of SP from the neuronal cells incubated with the nociceptin-LH_N/A fusion protein was assayed in comparison to (i) LH_N/A-only treated cells and (ii) cells
30 treated with media alone. This allowed the % inhibition of substance P from the eDRG to be calculated. The ability of the nociceptin-LH_N/A fusion protein to inhibit SP release (relative to cells treated with media alone) was reported in Table 1. The

data represent the mean of 3 determinations:

Table 1

Test Material (μM)	nociceptin-LH _N /A fusion protein	LH _N /A-only
	% Inhibition	% Inhibition
1.0	47.3	25.6
0.1	13.8	-11.5

5

Example 16 - Confirmation of ORL₁ receptor activation by measuring forskolin-stimulated cAMP production

Confirmation that a given TM is acting via the ORL₁ receptor is provided by the
 10 following test, in which the TMs ability to inhibit forskolin-stimulated cAMP production is assessed.

Materials

[³H]adenine and [¹⁴C]cAMP are obtained from GE Healthcare

15

Methods

The test is conducted essentially as described previously by Meunier *et al.* [Isolation and structure of the endogenous agonist of opioid receptor-like ORL₁ receptor. Nature 377: 532-535, 1995] in intact transfected-CHO cells plated on 24-well plastic
 20 plates.

To the cells is added [³H]adenine (1.0 μCi) in 0.4 ml of culture medium. The cells remain at 37°C for 2 h to allow the adenine to incorporate into the intracellular ATP pool. After 2 h, the cells are washed once with incubation buffer containing: 130 mM
 25 NaCl, 4.8 mM KCl, 1.2 mM KH₂PO₄, 1.3 mM CaCl₂, 1.2 mM MgSO₄, 10 mM glucose, 1 mg/ml bovine serum albumin and 25 mM HEPES, pH 7.4, and replaced with buffer containing forskolin (10 μM) and isobutylmethylxanthine (50 μM) with or without the

TM of interest. After 10 min., the medium is aspirated and replaced with 0.5 ml, 0.2 M HCl. Approximately 1000 cpm of [^{14}C]cAMP is added to each well and used as an internal standard. The contents of the wells are then transferred to columns of 0.65 g dry-alumina powder. The columns are eluted with 4 ml of 5 mM HCl, 0.5 ml of 0.1 M ammonium acetate, then two additional millilitres of ammonium acetate. The final eluate is collected into scintillation vials and counted for ^{14}C and tritium. Amounts collected are corrected for recovery of [^{14}C]cAMP. TMs that are agonists at the ORL₁ receptor cause a reduction in the level of cAMP produced in response to forskolin.

Example 17 - Confirmation of ORL₁ receptor activation using a GTP γ S binding functional assay

Confirmation that a given TM is acting via the ORL₁ receptor is also provided by the following test, a GTP γ S binding functional assay.

Materials

[^{35}S]GTP γ S is obtained from GE Healthcare

Wheatgerm agglutinin-coated (SPA) beads are obtained from GE Healthcare

Methods

This assay is carried out essentially as described by Traynor and Nahorski [Modulation by μ -opioid agonists of guanosine-5'-O-(3-[^{35}S]thio)triphosphate binding to membranes from human neuroblastoma SH-SY5Y cells. Mol. Pharmacol. 47: 848-854, 1995].

Cells are scraped from tissue culture dishes into 20 mM HEPES, 1 mM ethylenediaminetetraacetic acid, then centrifuged at $500 \times g$ for 10 min. Cells are resuspended in this buffer and homogenized with a Polytron Homogenizer.

The homogenate is centrifuged at $27,000 \times g$ for 15 min., and the pellet resuspended in buffer A, containing: 20 mM HEPES, 10 mM MgCl_2 , 100 mM NaCl,

pH 7.4. The suspension is recentrifuged at $20,000 \times g$ and suspended once more in buffer A. For the binding assay, membranes (8-15 μg protein) are incubated with [^{35}S]GTP S (50 pM), GDP (10 μM), with and without the TM of interest, in a total volume of 1.0 ml, for 60 min. at 25°C . Samples are filtered over glass fibre filters and counted as described for the binding assays.

Example 18 - Preparation of a LC/A and H_N/A backbone clones

The following procedure creates the LC and H_N fragments for use as the component backbone for multidomain fusion expression. This example is based on preparation of a serotype A based clone (SEQ ID27 and SEQ ID28), though the procedures and methods are equally applicable to the other serotypes [illustrated by the sequence listing for serotype B (SEQ ID29 and SEQ ID30) and serotype C (SEQ ID31 and SEQ ID32)].

Preparation of cloning and expression vectors

pCR 4 (Invitrogen) is the chosen standard cloning vector, selected due to the lack of restriction sequences within the vector and adjacent sequencing primer sites for easy construct confirmation. The expression vector is based on the pMAL (NEB) expression vector, which has the desired restriction sequences within the multiple cloning site in the correct orientation for construct insertion (*Bam*HI-*Sall*-*Pst*I-*Hind*III).

A fragment of the expression vector has been removed to create a non-mobilisable plasmid and a variety of different fusion tags have been inserted to increase purification options.

Preparation of protease (e.g. LC/A) insert

The LC/A (SEQ ID27) is created by one of two ways:

The DNA sequence is designed by back translation of the LC/A amino acid sequence [obtained from freely available database sources such as GenBank (accession number P10845) or Swissprot (accession locus BXA1_CLOBO) using one of a variety of reverse translation software tools (for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon))].

*Bam*HI/*Sal*I recognition sequences are incorporated at the 5' and 3' ends respectively of the sequence, maintaining the correct reading frame. The DNA sequence is screened (using software such as MapDraw, DNASTAR Inc.) for restriction-enzyme cleavage sequences incorporated during the back translation.

5 Any cleavage sequences that are found to be common to those required by the cloning system are removed manually from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to
10 published codon usage tables (for example GenBank Release 143, 13 September 2004). This optimised DNA sequence containing the LC/A open reading frame (ORF) is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.

15 The alternative method is to use PCR amplification from an existing DNA sequence with *Bam*HI and *Sal*I restriction enzyme sequences incorporated into the 5' and 3' PCR primers respectively. Complementary oligonucleotide primers are chemically synthesised by a supplier (for example MWG or Sigma-Genosys), so that each pair has the ability to hybridize to the opposite strands (3' ends pointing "towards" each
20 other) flanking the stretch of *Clostridium* target DNA, one oligonucleotide for each of the two DNA strands. To generate a PCR product the pair of short oligonucleotide primers specific for the *Clostridium* DNA sequence are mixed with the *Clostridium* DNA template and other reaction components and placed in a machine (the 'PCR machine') that can change the incubation temperature of the reaction tube
25 automatically, cycling between approximately 94°C (for denaturation), 55°C (for oligonucleotide annealing), and 72°C (for synthesis). Other reagents required for amplification of a PCR product include a DNA polymerase (such as *Taq* or *Pfu* polymerase), each of the four nucleotide dNTP building blocks of DNA in equimolar amounts (50-200 µM) and a buffer appropriate for the enzyme optimised for Mg²⁺
30 concentration (0.5-5 mM).

The amplification product is cloned into pCR 4 using either, TOPO TA cloning for *Taq* PCR products or Zero Blunt TOPO cloning for *Pfu* PCR products (both kits commercially available from Invitrogen). The resultant clone is checked by sequencing. Any additional restriction sequences which are not compatible with the cloning system are then removed using site directed mutagenesis [for example, using Quickchange (Stratagene Inc.)].

Preparation of translocation (e.g. H_N) insert

The H_N/A (SEQ ID28) is created by one of two ways:

- 10 The DNA sequence is designed by back translation of the H_N/A amino acid sequence [obtained from freely available database sources such as GenBank (accession number P10845) or Swissprot (accession locus BXA1_CLOBO)] using one of a variety of reverse translation software tools [for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)].
- 15 A *Pst*I restriction sequence added to the N-terminus and *Xba*I-stop codon-*Hind*III to the C-terminus ensuring the correct reading frame is maintained. The DNA sequence is screened (using software such as MapDraw, DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any sequences that are found to be common to those required by the cloning system are removed manually from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, 13 September 2004). This optimised DNA sequence is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.
- 20
- 25

- The alternative method is to use PCR amplification from an existing DNA sequence with *Pst*I and *Xba*I-stop codon-*Hind*III restriction enzyme sequences incorporated into the 5' and 3' PCR primers respectively. The PCR amplification is performed as described above. The PCR product is inserted into pCR 4 vector and checked by
- 30

sequencing. Any additional restriction sequences which are not compatible with the cloning system are then removed using site directed mutagenesis [for example using Quickchange (Stratagene Inc.)].

5 **Example 19 – Preparation of a LC/A-nociceptin-H_N/A fusion protein (nociceptin is N-terminal of the H_N-chain)**

Preparation of linker-nociceptin-spacer insert

The LC-H_N linker can be designed from first principle, using the existing sequence
10 information for the linker as the template. For example, the serotype A linker (in this case defined as the inter-domain polypeptide region that exists between the cysteines of the disulphide bridge between LC and H_N) is 23 amino acids long and has the sequence VRGIITSKTKSLDKGYNKALNDL. Within this sequence, it is understood that proteolytic activation in nature leads to an H_N domain that has an N-
15 terminus of the sequence ALNDL. This sequence information is freely available from available database sources such as GenBank (accession number P10845) or Swissprot (accession locus BXA1_CLOBO). Into this linker a Factor Xa site, nociceptin and spacer are incorporated; and using one of a variety of reverse translation software tools [for example EditSeq best *E. coli* reverse translation
20 (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)], the DNA sequence encoding the linker-ligand-spacer region is determined. Restriction sites are then incorporated into the DNA sequence and can be arranged as *Bam*HI-*Sall*-linker-protease site-nociceptin-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hind*III (SEQ ID33). It is important to ensure the correct reading frame is maintained for the spacer,
25 nociceptin and restriction sequences and that the *Xba*I sequence is not preceded by the bases, TC, which would result on DAM methylation. The DNA sequence is screened for restriction sequence incorporation, and any additional sequences are removed manually from the remaining sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software
30 programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example, GenBank Release 143, 13 September 2004). This optimised

DNA sequence is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.

-Preparation of the LC/A-nociceptin-H_N/A-fusion

- 5 In order to create the LC-linker-nociceptin-spacer-H_N construct (SEQ ID39), the pCR 4 vector encoding the linker (SEQ ID33) is cleaved with *Bam*HI + *Sall* restriction enzymes. This cleaved vector then serves as the recipient vector for insertion and ligation of the LC/A DNA (SEQ ID27) cleaved with *Bam*HI + *Sall*. The resulting plasmid DNA is then cleaved with *Pst*II + *Xba*I restriction enzymes and serves as the
- 10 recipient vector for the insertion and ligation of the H_N/A DNA (SEQ ID28) cleaved with *Pst*II + *Xba*I. The final construct contains the LC-linker-nociceptin-spacer-H_N ORF (SEQ ID39) for transfer into expression vectors for expression to result in a fusion protein of the sequence illustrated in SEQ ID40.

15 **Example 20 – Preparation of a nociceptin-LC/A-H_N/A fusion protein (nociceptin is N-terminal of the LC-chain)**

- The LC/A-H_N/A backbone is constructed as described in Example 19 using the synthesised A serotype linker with the addition of a Factor Xa site for activation,
- 20 arranged as *Bam*HI-*Sall*-linker-protease site-linker-*Pst*II-*Xba*I-stop codon-*Hind*III (SEQ ID34). The LC/A-H_N/A backbone and the synthesised N-terminal presentation nociceptin insert (SEQ ID35) are cleaved with *Bam*HI + *Hind*III restriction enzymes, gel purified and ligated together to create a nociceptin-spacer-LC-linker-H_N. The ORF (SEQ ID41) is then cut out using restriction enzymes *Ava*I + *Xba*I for transfer
- 25 into expression vectors for expression to result in a fusion protein of the sequence illustrated in SEQ ID42.

Example 21 – Preparation of a LC/C-nociceptin-H_N/C fusion protein

- 30 Following the methods used in Examples 1 and 2, the LC/C (SEQ ID31) and H_N/C (SEQ ID32) are created and inserted into the C serotype linker arranged as *Bam*HI-*Sall*-linker-protease site-nociceptin-*Nhe*I-spacer-*Spe*I-*Pst*II-*Xba*I-stop codon-*Hind*III.

(SEQ ID36). The final construct contains the LC-linker-nociceptin-spacer-H_N ORF (SEQ ID43) for expression as a protein of the sequence illustrated in SEQ ID44.

Example 22 - Preparation of a LC/C-nociceptin-H_N/C fusion protein with a serotype A activation sequence

Following the methods used in Examples 1 and 2, the LC/C (SEQ ID31) and H_N/C (SEQ ID32) are created and inserted into the A serotype linker arranged as *Bam*HI-*Sal*I-linker-protease site-nociceptin-*Nhe*I-spacer-*Spe*I-*Pst*II-*Xba*I-stop codon-*Hind*III (SEQ ID33). The final construct contains the LC-linker-nociceptin-spacer-H_N ORF (SEQ ID45) for expression as a protein of the sequence illustrated in SEQ ID46.

Example 23 - Preparation of a LC/A-met enkephalin-H_N/A fusion protein

Due to the small, five-amino acid, size of the met-enkephalin ligand the LC/A-met enkephalin-H_N/A fusion is created by site directed mutagenesis [for example using Quickchange (Stratagene Inc.)] using the LC/A-nociceptin-H_N/A fusion (SEQ ID39) as a template. Oligonucleotides are designed encoding the YGGFM met-enkephalin peptide, ensuring standard *E.coli* codon usage is maintained and no additional restriction sites are incorporated, flanked by sequences complimentary to the linker region of the LC/A-nociceptin-H_N/A fusion (SEQ ID39) either side on the nociceptin section. The SDM product is checked by sequencing and the final construct containing the LC-linker-met enkephalin-spacer-H_N ORF (SEQ ID47) for expression as a protein of the sequence illustrated in SEQ ID48.

Example 24 - Preparation of a LC/A-β endorphin-H_N/A fusion protein

Following the methods used in Examples 1 and 2, the LC/A (SEQ ID27) and H_N/A (SEQ ID28) are created and inserted into the A serotype β endorphin linker arranged as *Bam*HI-*Sal*I-linker-protease site-β endorphin-*Nhe*I-spacer-*Spe*I-*Pst*II-*Xba*I-stop codon-*Hind*III (SEQ ID37). The final construct contains the LC-linker-β endorphin-

spacer-H_N ORF (SEQ ID49) for expression as a protein of the sequence illustrated in SEQ ID50.

~~Example 25~~ -- Preparation of a LC/A-nociceptin variant-H_N/A fusion protein

5

Following the methods used in Examples 1 and 2, the LC/A (SEQ ID27) and H_N/A (SEQ ID28) are created and inserted into the A serotype nociceptin variant linker arranged as *Bam*HI-*Sall*-linker-protease site-nociceptin variant-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hind*III (SEQ ID38). The final construct contains the LC-
10 linker-nociceptin variant-spacer-H_N ORF (SEQ ID51) for expression as a protein of the sequence illustrated in SEQ ID52.

Example 26 – Purification method for LC/A-nociceptin-H_N/A fusion protein

15 --Defrost falcon tube containing 25 ml 50 mM HEPES pH 7.2; 200 mM NaCl and approximately 10 g of *E. coli* BL21 cell paste. Make the thawed cell paste up to 80 ml with 50 mM HEPES pH 7.2, 200 mM NaCl and sonicate on ice 30 seconds on, 30 seconds off for 10 cycles at a power of 22 microns ensuring the sample remains cool. Spin the lysed cells at 18 000 rpm, 4°C for 30 minutes. Load the supernatant
20 onto a 0.1 M NiSO₄ charged Chelating column (20-30 ml column is sufficient) equilibrated with 50 mM HEPES pH 7.2, 200 mM NaCl. Using a step gradient of 10 and 40 mM imidazol, wash away the non-specific bound protein and elute the fusion protein with 100 mM imidazol. Dialyse the eluted fusion protein against 5 L of 50 mM HEPES pH 7.2, 200 mM NaCl at 4°C overnight and measure the OD of the
25 dialysed fusion protein. Add 1 unit of factor Xa per 100 µg fusion protein and Incubate at 25°C static overnight. Load onto a 0.1 M NiSO₄ charged Chelating column (20-30 ml column is sufficient) equilibrated with 50 mM HEPES pH 7.2, 200 mM NaCl. Wash column to baseline with 50 mM HEPES pH 7.2, 200 mM NaCl. Using a step gradient of 10 and 40 mM imidazol, wash away the non-specific bound
30 protein and elute the fusion protein with 100 mM imidazol. Dialyse the eluted fusion protein against 5 L of 50 mM HEPES pH 7.2, 200 mM NaCl at 4°C overnight and

concentrate the fusion to about 2 mg/ml, aliquot sample and freeze at -20°C. Test purified protein using OD, BCA, purity analysis and SNAP-25 assessments.

Example 27 – Preparation of a LC/A-nociceptin-H_N/A fusion protein (nociceptin is N-terminal of the H_N-chain)

The linker-nociceptin-spacer insert is prepared as described in Example 19.

Preparation of the LC/A-nociceptin-H_N/A fusion

- 10 In order to create the LC-linker-nociceptin-spacer-H_N construct (SEQ ID39), the pCR 4 vector encoding the linker (SEQ ID33) is cleaved with *Bam*HI + *Sall* restriction enzymes. This cleaved vector then serves as the recipient for insertion and ligation of the LC/A DNA (SEQ ID27) also cleaved with *Bam*HI + *Sall*. The resulting plasmid DNA is then cleaved with *Bam*HI + *Hind*III restriction enzymes and the LC/A-linker
- 15 fragment inserted into a similarly cleaved vector containing a unique multiple cloning site for *Bam*HI, *Sall*, *Pst*I, and *Hind*III such as the pMAL vector (NEB). The H_N/A DNA (SEQ ID28) is then cleaved with *Pst*I + *Hind*III restriction enzymes and inserted into the similarly cleaved pMAL-LC/A-linker construct. The final construct contains the LC-linker-nociceptin-spacer-H_N ORF (SEQ ID39) for expression as a protein of
- 20 the sequence illustrated in SEQ ID40.

Example 28 – Preparation of a nociceptin-LC/A-H_N/A fusion protein (nociceptin is N-terminal of the LC-chain)

- 25 In order to create the nociceptin-spacer-LC/A-H_N/A construct, an A serotype linker with the addition of a Factor Xa site for activation, arranged as *Bam*HI-*Sall*-linker-protease site-linker-*Pst*I-*Xba*I-stop codon-*Hind*III (SEQ ID34) is synthesised as described in Example 27. The pCR 4 vector encoding the linker is cleaved with *Bam*HI + *Sall* restriction enzymes. This cleaved vector then serves as the recipient
- 30 for insertion and ligation of the LC/A DNA (SEQ ID27) also cleaved with *Bam*HI + *Sall*. The resulting plasmid DNA is then cleaved with *Bam*HI + *Hind*III restriction

enzymes and the LC/A-linker fragment inserted into a similarly cleaved vector containing the synthesised N-terminal presentation nociceptin insert (SEQ ID35).

This construct is then cleaved with *AvaI* + *HindIII* and inserted into an expression
- vector such as the pMAL-plasmid (NEB). The H_N/A DNA (SEQ ID28) is then cleaved
5 with *PstI* + *HindIII* restriction enzymes and inserted into the similarly cleaved pMAL-
nociceptin-LC/A-linker construct. The final construct contains the nociceptin-spacer-
LC/A-H_N/A ORF (SEQ ID63) for expression as a protein of the sequence illustrated
in SEQ ID64.

10 **Example 29 - Preparation and purification of an LC/A-nociceptin-H_N/A fusion protein family with variable spacer length**

Using the same strategy as employed in Example 19, a range of DNA linkers were prepared that encoded nociceptin and variable spacer content. Using one of a
15 variety of reverse translation software tools [for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)], the DNA sequence encoding the linker-ligand-spacer region is determined. Restriction sites are then incorporated into the DNA sequence and can be arranged as *BamHI-SalI*-linker-protease site-nociceptin-*NheI*-spacer-*SpeI-PstI-XbaI*-stop codon-*HindIII* (SEQ
20 ID65 to SEQ ID69). It is important to ensure the correct reading frame is maintained for the spacer, nociceptin and restriction sequences and that the *XbaI* sequence is not preceded by the bases, TC which would result on DAM methylation. The DNA sequence is screened for restriction sequence incorporation and any additional sequences are removed manually from the remaining sequence ensuring common
25 *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, 13 September 2004). This optimised DNA sequence is then commercially synthesized (for example by
30 Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.

The spacers that were created included:

Table 2

<u>Code</u>	<u>Protein sequence of the linker</u>	<u>SEQ ID of the linker-DNA</u>
GS10	ALAGGGGSALVLQ	53
GS15	ALAGGGGSGGGGSALVLQ	54
GS25	ALAGGGGSGGGGSGGGGSGGGGSALVLQ	55
GS30	ALAGGGGSGGGGSGGGGSGGGGSGGGGSALVLQ	56
HX27	ALAAEAAAKEAAAKEAAAKAGGGGSALVLQ	57

By way of example, in order to create the LC/A-CPN(GS15)-H_N/A fusion construct (SEQ ID70), the pCR 4 vector encoding the linker (SEQ ID66) is cleaved with *Bam*HI + *Sa*II restriction enzymes. This cleaved vector then serves as the recipient vector for insertion and ligation of the LC/A DNA (SEQ ID27) also cleaved with *Bam*HI + *Sa*II. The resulting plasmid DNA is then cleaved with *Bam*HI + *Hind*III restriction enzymes and the LC/A-linker fragment inserted into a similarly cleaved vector containing a unique multiple cloning site for *Bam*HI, *Sa*II, *Pst*I, and *Hind*III such as the pMAL vector (NEB). The H_N/A DNA (SEQ ID28) is then cleaved with *Pst*I + *Hind*III restriction enzymes and inserted into the similarly cleaved pMAL-LC/A-linker construct. The final construct contains the LC/A-CPN(GS15)-H_N/A ORF (SEQ ID70) for expression as a protein of the sequence illustrated in SEQ ID71.

15

As a further example, to create the LC/A-CPN(GS25)-H_N/A fusion construct (SEQ ID72), the pCR 4 vector encoding the linker (SEQ ID67) is cleaved with *Bam*HI + *Sa*II restriction enzymes. This cleaved vector then serves as the recipient vector for insertion and ligation of the LC/A DNA (SEQ ID27) cleaved with *Bam*HI + *Sa*II. The resulting plasmid DNA is then cleaved with *Bam*HI + *Hind*III restriction enzymes and the LC/A-linker fragment inserted into a similarly cleaved vector containing a unique multiple cloning site for *Bam*HI, *Sa*II, *Pst*I, and *Hind*III such as the pMAL vector (NEB). The H_N/A DNA (SEQ ID28) is then cleaved with *Pst*I + *Hind*III restriction enzymes and inserted into the similarly cleaved pMAL-LC/A-linker construct. The

20

final construct contains the LC/A-CPN(GS25)-H_N/A ORF (SEQ ID72) for expression as a protein of the sequence illustrated in SEQ ID73.

5 Variants of the LC/A-CPN-H_N/A fusion consisting of GS10, GS30 and HX27 are similarly created. Using the purification methodology described in Example 26, fusion protein is purified from *E. coli* cell paste. Figure 12 illustrates the purified product obtained in the case of LC/A-CPN(GS10)-H_N/A, LC/A-CPN(GS15)-H_N/A, LC/A-CPN(GS25)-H_N/A, LC/A-CPN(GS30)-H_N/A and LC/A-CPN(HX27)-H_N/A.

10 **Example 30 - Assessment of *in vitro* efficacy of an LC/A-nociceptin-H_N/A fusion**

Fusion protein prepared according to Examples 2 and 9 was assessed in the eDRG neuronal cell model.

15 Assays for the inhibition of substance P release and cleavage of SNAP-25 have been previously reported (Duggan *et al.*, 2002, *J. Biol. Chem.*, 277, 34846-34852). Briefly, dorsal root ganglia neurons are harvested from 15-day-old fetal Sprague-Dawley rats and dissociated cells plated onto 24-well plates coated with Matrigel at a density of 1×10^6 cells/well. One day post-plating the cells are treated with 10 μ M cytosine β -D-arabinofuranoside for 48 h. Cells are maintained in Dulbecco's minimal essential medium supplemented with 5% heat-inactivated fetal bovine serum, 5 mM L-glutamine, 0.6% D-glucose, 2% B27 supplement, and 100 ng/ml 2.5S mouse nerve growth factor. Cultures are maintained for 2 weeks at 37°C in 95% air/5% CO₂ before addition of test materials.

25 Release of substance P from eDRG is assessed by enzyme-linked immunosorbent assay. Briefly, eDRG cells are washed twice with low potassium-balanced salt solution (BSS: 5 mM KCl, 137 mM NaCl, 1.2 mM MgCl₂, 5 mM glucose, 0.44 mM KH₂PO₄, 20 mM HEPES, pH 7.4, 2 mM CaCl₂). Basal samples are obtained by incubating each well for 5 min. with 1 ml of low potassium BSS. After removal of this

buffer, the cells are stimulated to release by incubation with 1 ml of high potassium buffer (BSS as above with modification to include 100 mM KCl isotonicity balanced with NaCl) for 5 min. All samples are removed to tubes on ice prior to assay of substance P. Total cell lysates are prepared by addition of 250- μ l of 2 M acetic acid/0.1% trifluoroacetic acid to lyse the cells, centrifugal evaporation, and resuspension in 500 μ l of assay buffer. Diluted samples are assessed for substance P content. Substance P immunoreactivity is measured using Substance P Enzyme Immunoassay Kits (Cayman Chemical Company or R&D Systems) according to manufacturers' instructions. Substance P is expressed in pg/ml relative to a standard substance P curve run in parallel.

SDS-PAGE and Western blot analysis were performed using standard protocols (Novex). SNAP-25 proteins were resolved on a 12% Tris/glycine polyacrylamide gel (Novex) and subsequently transferred to nitrocellulose membrane. The membranes were probed with a monoclonal antibody (SMI-81) that recognises cleaved and intact SNAP-25. Specific binding was visualised using peroxidase-conjugated secondary antibodies and a chemiluminescent detection system. Cleavage of SNAP-25 was quantified by scanning densitometry (Molecular Dynamics Personal SI, ImageQuant data analysis software). Percent SNAP-25 cleavage was calculated according to the formula: $(\text{Cleaved SNAP-25}/(\text{Cleaved} + \text{Intact SNAP-25})) \times 100$.

Following exposure of eDRG neurons to an LC/A-nociceptin- H_N /A fusion (termed CPN-A), both inhibition of substance P release and cleavage of SNAP-25 are observed (Figure 13). After 24 h exposure to the fusion, 50% of maximal SNAP-25 cleavage is achieved by a fusion concentration of 6.3 ± 2.5 nM.

The effect of the fusion is also assessed at defined time points following a 16 h exposure of eDRG to CPN-A. Figure 14 illustrates the prolonged duration of action of the CPN-A fusion protein, with measurable activity still being observed at 28 days post exposure.

Example 31 - Assessment of *in vitro* efficacy of an LC/A-nociceptin variant-H_N/A fusion

5 Fusion protein prepared according to Examples 8 and 9 was assessed in the eDRG neuronal cell mode using the method described in Example 30.

Following exposure of eDRG neurons to an LC/A-nociceptin variant-H_N/A fusion (termed CPNv-A), both inhibition of substance P release and cleavage of SNAP-25 are observed. After 24 h exposure to the fusion, 50% of maximal SNAP-25 cleavage
10 is achieved by a fusion concentration of 1.4 ± 0.4 nM (Figure 15).

The effect of the fusion is also assessed at defined time points following a 16 h exposure of eDRG to CPN-A. Figure 16 illustrates the prolonged duration of action of the CPN-A fusion protein, with measurable activity still being observed at 24 days
15 post exposure.

The binding capability of the CPNv-A fusion protein is also assessed in comparison to the CPN-A fusion. Figure 17 illustrates the results of a competition experiment to determine binding efficacy at the ORL-1 receptor. CPNv-A is demonstrated to
20 displace [3H]-nociceptin, thereby confirming that access to the receptor is possible with the ligand in the central presentation format.

Example 32 - Preparation of an LC/A-nociceptin variant-H_N/A fusion protein that is activated by treatment with Enterokinase

25 Following the methods used in Examples 1 and 2, the LC/A (SEQ ID27) and H_N/A (SEQ ID28) are created and inserted into the A serotype nociceptin variant linker arranged as *Bam*HI-*Sal*I-linker-enterokinase protease site-nociceptin variant-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hind*III (SEQ ID74). The final construct contains
30 the LC-linker-nociceptin variant-spacer-H_N ORF sequences (SEQ ID75) for expression as a protein of the sequence illustrated in SEQ ID76. The fusion protein is termed CPNv(Ek)-A. Figure 18 illustrates the purification of CPNv(Ek)-A from *E.*

coli following the methods used in Example 26 but using Enterokinase for activation at 0.00064 µg per 100 µg of fusion protein.

Example 33 - Assessment of *in vitro* efficacy of an LC/A-nociceptin variant-H_N/A fusion that has been activated by treatment with enterokinase

The CPNv(Ek)-A prepared in Example 32 is obtained in a purified form and applied to the eDRG cell model to assess cleavage of SNAP-25 (using methodology from Example 30). Figure 19 illustrates the cleavage of SNAP-25 following 24 h exposure of eDRG to CPNv(Ek)-A. The efficiency of cleavage is observed to be similar to that achieved with the Factor Xa-cleaved material, as recorded in Example 31.

Example 34 - Preparation of an LC/C-nociceptin variant-H_N/C fusion protein with a Factor Xa activation linker derived from serotype A

Following the methods used in Example 21, the LC/C (SEQ ID31) and H_N/C (SEQ ID32) are created and inserted into the A serotype nociceptin variant linker arranged as *Bam*HI-*Sal*I-linker-nociceptin variant-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hind*III (SEQ ID77). The final construct contains the LC-linker-nociceptin variant-spacer-H_N ORF sequences (SEQ ID78) for expression as a protein of the sequence illustrated in SEQ ID79. The fusion protein is termed CPNv-C (act. A). Figure 20 illustrates the purification of CPNv-C (act. A) from *E. coli* following the methods used in Example 26.

Example 35 - Assessment of *in vitro* efficacy of an LC/C-nociceptin variant-H_N/C fusion protein

Following the methods used in Example 26, the CPNv-C (act. A) prepared in Example 34 is obtained in a purified form and applied to the eDRG cell model to assess cleavage of SNAP-25 (using methodology from Example 30). After 24 h exposure to the fusion, 50% of maximal syntaxin cleavage is achieved by a fusion concentration of 3.1±2.0 nM. Figure 21 illustrates the cleavage of syntaxin following

24 h exposure of eDRG to CPNv-C (act. A).

Example 36 - Assessment of *in vivo* efficacy of an LC/A-nociceptin-HN/A fusion-

5

The ability of an LC/A-nociceptin- H_N/A fusion (CPN/A) to inhibit acute capsaicin-induced mechanical allodynia is evaluated following subcutaneous intraplantar injection in the rat hind paw. Test animals are evaluated for paw withdrawal frequency (PWF%) in response to a 10 g Von Frey filament stimulus series (10 stimuli x 3 trials) prior to recruitment into the study, after subcutaneous treatment with CPN/A but before capsaicin, and following capsaicin challenge post-injection of CPN/A (average of responses at 15' and 30'). Capsaicin challenge is achieved by injection of 10 µL of a 0.3% solution. Sample dilutions are prepared in 0.5% BSA/saline. Figure 22 illustrates the reversal of mechanical allodynia that is achieved by pre-treatment of the animals with a range of concentrations of LC/A-nociceptin-HN/A fusion.

The ability of an LC/A-nociceptin-HN/A fusion (CPN/A) to inhibit streptozotocin (STZ)-induced mechanical (tactile) allodynia in rats is evaluated. STZ-induced mechanical allodynia in rats is achieved by injection of streptozotocin (i.p. or i.v.) which yields destruction of pancreatic β-cells leading to loss of insulin production, with concomitant metabolic stress (hyperglycemia and hyperlipidemia). As such, STZ induces Type I diabetes. In addition, STZ treatment leads to progressive development of neuropathy, which serves as a model of chronic pain with hyperalgesia and allodynia that may reflect signs observed in diabetic humans (peripheral diabetic neuropathy).

Male Sprague-Dawley rats (250-300 g) are treated with 65 mg/kg STZ in citrate buffer (I.V.) and blood glucose and lipid are measured weekly to define the readiness of the model. Paw Withdrawal Threshold (PWT) is measured in response to a Von Frey filament stimulus series over a period of time. Allodynia is said to be established when the PWT on two consecutive test dates (separated by 1 week)

measures below 6 g on the scale. At this point, rats are randomized to either a saline group (negative efficacy control), gabapentin group (positive efficacy control) or a test group (CPN/A). Test materials (20-25 μ l) are injected subcutaneously as a single injection (except gabapentin) and the PWT is measured at 1 day post-treatment and periodically thereafter over a 2-week period. Gabapentin (30 mg/kg i.p. @ 3 ml/kg injection volume) is injected daily, 2 hours prior to the start of PWT testing. Figure 23 illustrates the reversal of allodynia achieved by pre-treatment of the animals with 750 ng of CPN/A. Data were obtained over a 2-week period after a single injection of CPN/A

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Example 37 - Assessment of *in vivo* efficacy of an LC/A-nociceptin variant-H_N/A fusion

The ability of an LC/A-nociceptin variant-H_N/A fusion (CPNv/A) to inhibit capsaicin-induced mechanical allodynia is evaluated following subcutaneous intraplantar injection in the rat hind paw. Test animals are evaluated for paw withdrawal frequency (PWF%) in response to a 10 g Von Frey filament stimulus series (10 stimuli x 3 trials) prior to recruitment into the study (Pre-Treat); after subcutaneous intraplantar treatment with CPNv/A but before capsaicin (Pre-CAP); and following capsaicin challenge post-injection of CPNv/A (average of responses at 15' and 30'; CAP). Capsaicin challenge is achieved by injection of 10 μ L of a 0.3% solution. Sample dilutions are prepared in 0.5% BSA/saline.

Figure 24 illustrates the reversal of allodynia that is achieved by pre-treatment of the animals with a range of concentrations of LC/A-nociceptin variant-H_N/A fusion in comparison to the reversal achieved with the addition of LC/A-nociceptin-H_N/A fusion. These data are expressed as a normalized paw withdrawal frequency differential, in which the difference between the peak response (post-capsaicin) and the baseline response (pre-capsaicin) is expressed as a percentage. With this analysis, it can be seen that CPNv/A is more potent than CPN/A since a lower dose of CPNv/A is required to achieve similar analgesic effect to that seen with CPN/A.

Example 38 - Preparation of an LC/A-leu enkephalin-H_N/A fusion protein

Due to the small, five-amino acid, size of the leu-enkephalin ligand the LC/A-leu-enkephalin-H_N/A fusion is created by site directed mutagenesis [for example using Quickchange (Stratagene Inc.)] using the LC/A-nociceptin-H_N/A fusion (SEQ ID39) as a template. Oligonucleotides are designed encoding the YGGFL leu-enkephalin peptide, ensuring standard *E. coli* codon usage is maintained and no additional restriction sites are incorporated, flanked by sequences complimentary to the linker region of the LC/A-nociceptin-H_N/A fusion (SEQ ID39) either side on the nociceptin section. The SDM product is checked by sequencing and the final construct containing the LC-linker-leu enkephalin-spacer-H_N ORF (SEQ ID80) for expression as a protein of the sequence illustrated in SEQ ID81. The fusion protein is termed CPLE-A. Figure 25 illustrates the purification of CPLE-A from *E. coli* following the methods used in Example 26.

Example 39 – Expression and purification of an LC/A-beta-endorphin-H_N/A fusion protein

Following the methods used in Example 26, and with the LC/A-beta-endorphin-H_N/A fusion protein (termed CPBE-A) created in Example 24, the CPBE-A is purified from *E. coli*. Figure 26 illustrates the purified protein as analysed by SDS-PAGE.

Example 40 - Preparation of an LC/A-nociceptin mutant-H_N/A fusion protein

Due to the single amino acid modification necessary to mutate the nociceptin sequence at position 1 from a Phe to a Tyr, the LC/A-nociceptin mutant-H_N/A fusion is created by site directed mutagenesis [for example using Quickchange (Stratagene Inc.)] using the LC/A-nociceptin-H_N/A fusion (SEQ ID39) as a template. Oligonucleotides are designed encoding tyrosine at position 1 of the nociceptin sequence, ensuring standard *E. coli* codon usage is maintained and no additional restriction sites are incorporated, flanked by sequences complimentary to the linker region of the LC/A-nociceptin-H_N/A fusion (SEQ ID39) either side on the nociceptin

section. The SDM product is checked by sequencing and the final construct containing the LC/A-nociceptin mutant-spacer-H_N/A fusion ORF (SEQ ID82) for expression as a protein of the sequence illustrated in SEQ ID83. The fusion protein is termed CPOP-A. Figure 27 illustrates the purification of CPOP-A from *E. coli* following the methods used in Example 26.

Example 41 - Preparation and assessment of an LC/A-nociceptin variant mutant-H_N/A fusion protein

Due to the single amino acid modification necessary to mutate the nociceptin sequence at position 1 from a Phe to a Tyr, the LC/A-nociceptin variant mutant-H_N/A fusion is created by site directed mutagenesis [for example using Quickchange (Stratagene Inc.)] using the LC/A-nociceptin variant-H_N/A fusion (SEQ ID51) as a template. Oligonucleotides are designed encoding tyrosine at position 1 of the nociceptin sequence, ensuring standard *E. coli*-codon usage is maintained and no additional restriction sites are incorporated, flanked by sequences complimentary to the linker region of the LC/A-nociceptin variant-H_N/A fusion (SEQ ID51) either side on the nociceptin section. The SDM product is checked by sequencing and the final construct containing the LC/A-nociceptin mutant-spacer-H_N/A fusion ORF (SEQ ID84) for expression as a protein of the sequence illustrated in SEQ ID85. The fusion protein is termed CPOPv-A. Figure 28 illustrates the purification of CPOPv-A from *E. coli* following the methods used in Example 26.

Using methodology described in Example 30, CPOPv-A is assessed for its ability to cleave SNAP-25 in the eDRG cell model. Figure 29 illustrates that CPOPv-A is able to cleave SNAP-25 in the eDRG model, achieving cleavage of 50% of the maximal SNAP-25 after exposure of the cells to approximately 5.9 nM fusion for 24 h.

Example 42 - Preparation of an IgA protease-nociceptin variant-H_N/A fusion protein

The IgA protease amino acid sequence was obtained from freely available database

sources such as GenBank (accession number P09790). Information regarding the structure of the *N. Gonorrhoeae* IgA protease gene is available in the literature (Pohlner *et al.*, Gene structure and extracellular secretion of *Neisseria gonorrhoeae* IgA-protease, *Nature*, 1987, 325(6103), 458-62). Using Backtranslation tool v2.0 (Entelechon), the DNA sequence encoding the IgA protease modified for *E. coli* expression was determined. A *Bam*HI recognition sequence was incorporated at the 5' end and a codon encoding a cysteine amino acid and *Sal*I recognition sequence were incorporated at the 3' end of the IgA DNA. The DNA sequence was screened using MapDraw, (DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any cleavage sequences that are found to be common to those required for cloning were removed manually from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage was assessed Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables. This optimised DNA sequence (SEQ ID86) containing the IgA open reading frame (ORF) is then commercially synthesized.

The IgA (SEQ ID86) is inserted into the LC-linker-nociceptin variant-spacer-H_N ORF (SEQ ID51) using *Bam*HI and *Sal*I restriction enzymes to replace the LC with the IgA protease DNA. The final construct contains the IgA-linker-nociceptin variant-spacer-H_N ORF (SEQ ID87) for expression as a protein of the sequence illustrated in SEQ ID88.

Example 43 - Preparation and assessment of a nociceptin targeted endopeptidase fusion protein with a removable histidine purification tag.

DNA was prepared that encoded a Factor Xa removable his-tag (his6), although it is clear that alternative proteases site such as Enterokinase and alternative purification tags such as longer histidine tags are also possible. Using one of a variety of reverse translation software tools [for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)], the DNA sequence encoding the Factor Xa removable his-tag region is determined.

Restriction sites are then incorporated into the DNA sequence and can be arranged as *NheI*-linker-*SpeI*-*PstI*-*H_N*/A-*XbaI*-LEIEGRSGHHHHHStop codon-*HindIII* (SEQ ID89). The DNA sequence is screened for restriction sequence incorporated and any-additional sequences are removed manually from the remaining sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, 13 September 2004). This optimised DNA sequence is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector. In order to create CPNv-A-FXa-HT (SEQ ID90, removable his-tag construct) the pCR 4 vector encoding the removable his-tag is cleaved with *NheI* and *HindIII*. The *NheI* - *HindIII* fragment is then inserted into the LC/A-CPNv-*H_N*/A vector (SEQ ID51) that has also been cleaved by *NheI* and *HindIII*. The final construct contains the LC/A-linker-nociceptin variant-spacer-*H_N*-FXa-Histag-*HindIII* ORF sequences (SEQ ID90) for expression as a protein of the sequence illustrated in SEQ ID91. Figure 30 illustrates the purification of CPNv-A-FXa-HT from *E. coli* following the methods used in Example 26.

Example 44 - Preparation of a leu-enkephalin targeted endopeptidase fusion protein containing a translocation domain derived from diphtheria toxin

The DNA sequence is designed by back translation of the amino acid sequence of the translocation domain of the diphtheria toxin (obtained from freely available database sources such as GenBank (accession number 1XDTT) using one of a variety of reverse translation software tools [for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)]. Restriction sites are then incorporated into the DNA sequence and can be arranged as *NheI*-Linker-*SpeI*-*PstI*- diphtheria translocation domain-*XbaI*-stop codon-*HindIII* (SEQ ID92). *PstI*/*XbaI* recognition sequences are incorporated at the 5' and 3' ends of the translocation domain respectively of the sequence maintaining the correct reading frame. The DNA sequence is screened (using software such as MapDraw,

DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any cleavage sequences that are found to be common to those required by the cloning system are removed manually from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, 13 September 2004). This optimised DNA sequence containing the diphtheria translocation domain is then commercially synthesized as *NheI*-Linker-*SpeI*-*PstI*-diphtheria translocation domain-*XbaI*-stop codon-*HindIII* (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector (Invitrogen). The pCR 4 vector encoding the diphtheria translocation domain is cleaved with *NheI* and *XbaI*. The *NheI* – *XbaI* fragment is then inserted into the LC/A-CPLE-H_N/A vector (SEQ ID80) that has also been cleaved by *NheI* and *XbaI*. The final construct contains the LC/A-leu-enkephalin-spacer-diphtheria translocation domain ORF sequences (SEQ ID93) for expression as a protein of the sequence illustrated in SEQ ID94.

Example 45 - Preparation of a nociceptin variant targeted endopeptidase fusion protein containing a LC domain derived from tetanus toxin.

The DNA sequence is designed by back translation of the tetanus toxin LC amino acid sequence (obtained from freely available database sources such as GenBank (accession number X04436) using one of a variety of reverse translation software tools [for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)]. *Bam*HI/*Sa*I recognition sequences are incorporated at the 5' and 3' ends respectively of the sequence maintaining the correct reading frame (SEQ ID95). The DNA sequence is screened (using software such as MapDraw, DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any cleavage sequences that are found to be common to those required by the cloning system are removed manually from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E.*

coli codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release-143; 13 September 2004). This optimised DNA sequence containing the
5 tetanus toxin LC open reading frame (ORF) is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector (Invitrogen). The pCR 4 vector encoding the TeNT LC is cleaved with *Bam*HI and *Sal*I. The *Bam*HI – *Sal*I fragment is then inserted into the LC/A-CPNv-H_N/A vector (SEQ ID51) that has also been cleaved by *Bam*HI and *Sal*I. The final
10 construct contains the TeNT LC-linker-nociceptin variant-spacer-H_N ORF sequences (SEQ ID96) for expression as a protein of the sequence illustrated in SEQ ID97.

Example 46 - Preparation of an LC/C-nociceptin variant-H_N/C fusion protein with a native serotype C linker that is susceptible to Factor Xa cleavage

15 Following the methods used in Example 21, the LC/C (SEQ ID31) and H_N/C (SEQ ID32) are created and inserted into the C serotype nociceptin variant linker arranged as *Bam*HI-*Sal*I-linker-nociceptin variant-*Nhe*I-spacer-*Spe*I-*Pst*II-*Xba*I-stop codon-*Hind*III (SEQ ID98). The final construct contains the LC-linker-nociceptin variant-
20 spacer-H_N ORF sequences (SEQ ID99) for expression as a protein of the sequence illustrated in SEQ ID100. The fusion protein is termed CPNv-C (act. C).

Claims:

1. A non-cytotoxic protein conjugate for inhibition or reduction of exocytic fusion
in a nociceptive sensory afferent cell, comprising:

5

- (i) Targeting Moiety (TM),

10

wherein said TM is an agonist of a receptor present on said
nociceptive sensory afferent cell, and wherein said receptor
undergoes endocytosis to be incorporated into an endosome
within the nociceptive sensory afferent cell;

- (ii) a non-cytotoxic protease or a fragment thereof,

15

wherein the protease or protease fragment is capable of
cleaving a protein of the exocytic fusion apparatus of said
nociceptive sensory afferent cell; and

- (iii) a Translocation Domain,

20

wherein the Translocation Domain translocates the protease or
protease fragment from within the endosome, across the
endosomal membrane, and into the cytosol of the nociceptive
sensory afferent cell.

25

2. The non-cytotoxic conjugate of Claim 1, wherein the receptor is an ORL₁
receptor.

30

3. The non-cytotoxic conjugate of Claim 1 or 2, wherein the TM has at least
70% or at least 80 % homology to SEQ ID No. 2 or a fragment thereof.

4. The non-cytotoxic conjugate of Claim 1 or 2, wherein the TM has at least 90% homology to SEQ ID No. 2 or a fragment thereof.
- ~~5. The non-cytotoxic conjugate of Claim 1 or Claim 2; wherein the TM has at~~
5 least 95% homology to SEQ ID No. 2 or a fragment thereof.
6. The non-cytotoxic conjugate of Claim 1 or 2, wherein the TM is SEQ ID No. 2 or a fragment thereof.
- 10 7. The non-cytotoxic conjugate of Claim 1 or 2, wherein the TM is nociceptin.
8. The non-cytotoxic conjugate of Claim 1 or 2, wherein the TM is selected from the group consisting of SEQ ID Nos. 4, 6, 8, 10, 12, 14.
- 15 9. The non-cytotoxic conjugate of any preceding claim, wherein the non-cytotoxic protease is a bacterial protein, or a fragment thereof, capable of cleaving a protein of the exocytic fusion apparatus of the nociceptive sensory afferent cell.
- 20 10. The non-cytotoxic conjugate of Claim 9, wherein the non-cytotoxic protease is selected from a clostridial neurotoxin, or an IgA protease.
11. The non-cytotoxic conjugate of any preceding claim, wherein the Translocation Domain is derived from a clostridial source.
- 25 12. The non-cytotoxic conjugate of Claim 11, wherein the Translocation Domain is a botulinum H_N domain.
13. The non-cytotoxic conjugate of any preceding claim, wherein the nociceptive
30 sensory afferent cell is a primary nociceptive sensory afferent cell.

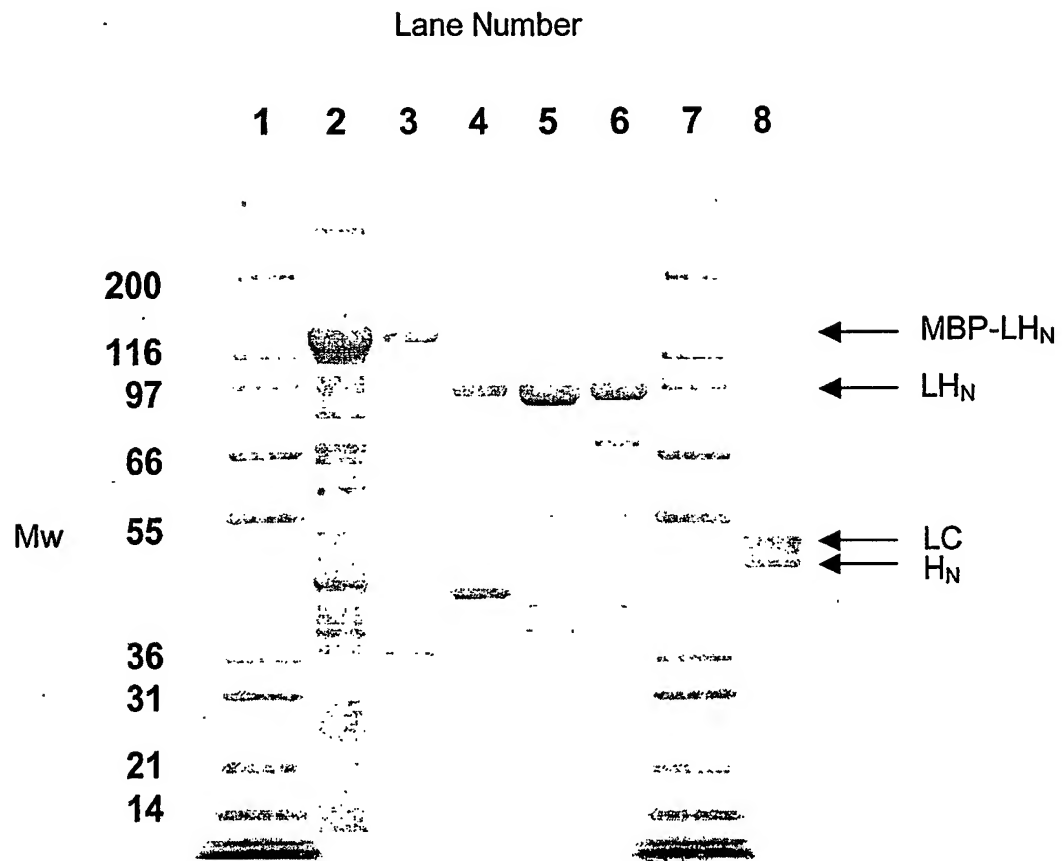
14. The non-cytotoxic conjugate according to Claim 1, wherein said conjugate comprises an amino acid sequence selected from the group consisting of SEQ ID NOs 14, 16, 18, 20, 22, 24, and 26.
- 5 15. A non-cytotoxic conjugate for inhibition or reduction of exocytotic fusion in a nociceptive sensory afferent cell, comprising:
- (i) a Targeting Moiety (TM),
- 10 wherein said TM is an agonist of a receptor present on said nociceptive sensory afferent cell, and wherein said receptor undergoes endocytosis to be incorporated into an endosome within the nociceptive sensory afferent cell;
- 15 (ii) a DNA sequence encoding a non-cytotoxic protease or a fragment thereof,
- wherein the DNA sequence is expressible in the nociceptive sensory afferent cell and when so expressed provides a
- 20 protease or protease fragment capable of cleaving a protein of the exocytic fusion apparatus of said nociceptive sensory afferent cell; and
- (iii) a Translocation Domain,
- 25 wherein the Translocation Domain translocates the DNA sequence encoding the protease or protease fragment from within the endosome, across the endosomal membrane, and into the nociceptive sensory afferent cell.
- 30 16. The non-cytotoxic conjugate of Claim 15, wherein the receptor is an ORL₁ receptor.

17. The non-cytotoxic conjugate of Claim 15 or 16, wherein the TM has at least 70% or at least 80% homology to SEQ ID No. 2 or a fragment thereof.
- 5 18. The non-cytotoxic conjugate of Claim 15 or 16, wherein the TM has at least 90% homology to SEQ ID No. 2 or a fragment thereof.
19. The non-cytotoxic conjugate of Claim 15 or Claim 16, wherein the TM has at least 95% homology to SEQ ID No. 2 or a fragment thereof.
- 10 20. The non-cytotoxic conjugate of Claim 15 or Claim 16, wherein the TM is SEQ ID No. 2 or a fragment thereof.
21. The non-cytotoxic conjugate of Claim 15 or Claim 16, wherein the TM is nociceptin.
- 15 22. The non-cytotoxic conjugate of Claim 15 or Claim 16, wherein the TM is selected from the group consisting of SEQ ID Nos. 4, 6, 8, 10, 12, 14.
- 20 23. The non-cytotoxic conjugate of Claim 15 or Claim 16, wherein the non-cytotoxic protease is a bacterial protein, or a fragment thereof, capable of cleaving a protein of the exocytic fusion apparatus of the nociceptive sensory afferent cell.
- 25 24. The non-cytotoxic conjugate of Claim 23, wherein the non-cytotoxic protease is selected from a clostridial neurotoxin, or an IgA protease.
25. The non-cytotoxic conjugate of Claim 15 or Claim 16, wherein the Translocation Domain is derived from a clostridial source.
- 30 26. The non-cytotoxic conjugate of Claim 25, wherein the Translocation Domain is a botulinum H_N domain.

27. The non-cytotoxic conjugate of Claim 15 or 16, wherein the nociceptive sensory afferent cell is a primary nociceptive sensory afferent cell.
- 5 28. The non-cytotoxic conjugate of any of Claims 1 to 14, wherein the TM, the Translocation Domain and the protease or fragment thereof are covalently linked.
- 10 29. The non-cytotoxic conjugate of any of Claims 15 to 27, wherein the TM, the Translocation Domain and the DNA sequence encoding the protease or fragment thereof, are covalently linked.
30. A pharmaceutical composition, comprising a conjugate according to any of Claims 1 to 29 and a pharmaceutically acceptable carrier.
- 15 31. A DNA construct encoding the conjugate of any of Claims 1 to 14.
32. A DNA construct according to Claim 31, wherein the construct comprises a DNA sequence selected from SEQ ID NOs 13, 15, 17, 19, 21, 23, and 25.
- 20 33. A method of preparing the conjugate of any of Claims 1 to 14, comprising expressing the DNA construct of Claim 30 in a host cell.
34. A method for treating pain, comprising administering to a patient a conjugate according to any of Claim 1-29 or a composition according to Claim 30.
- 25 35. Use of a conjugate according to any of Claims 1-29 or a composition according to Claim 30, for the manufacture of a medicament for treating pain.

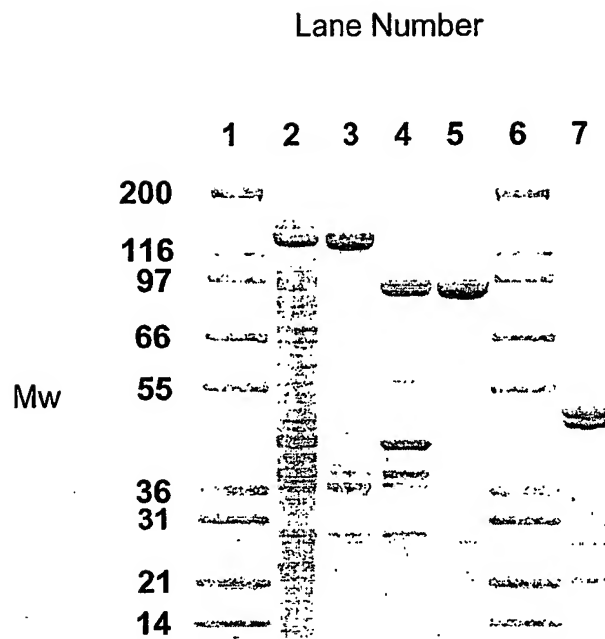
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Figure 1



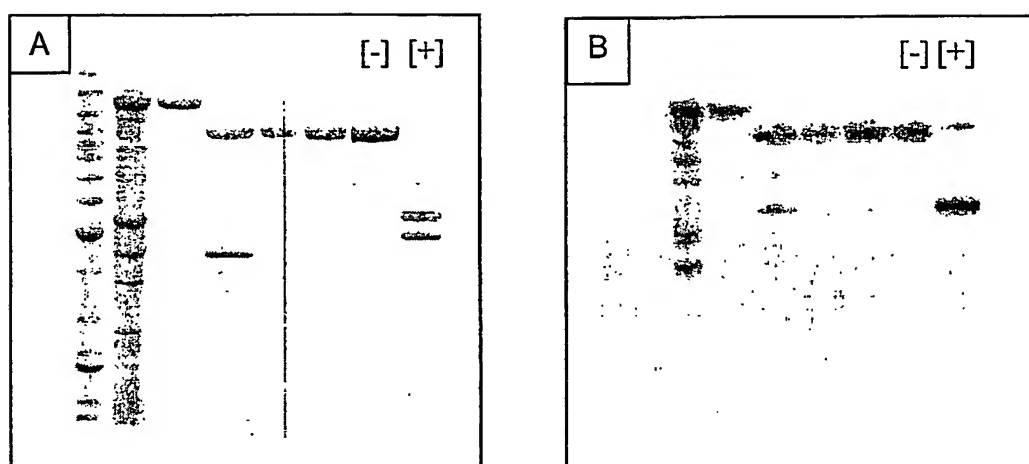
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Figure 2



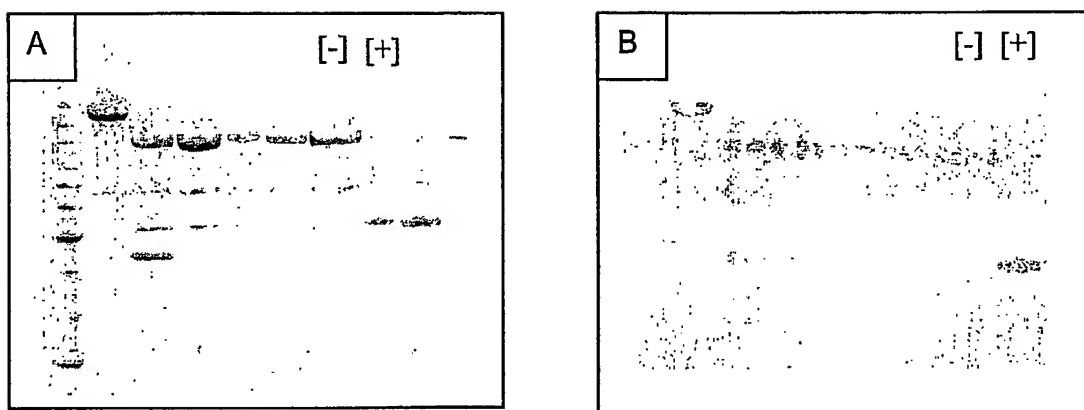
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Figure 3



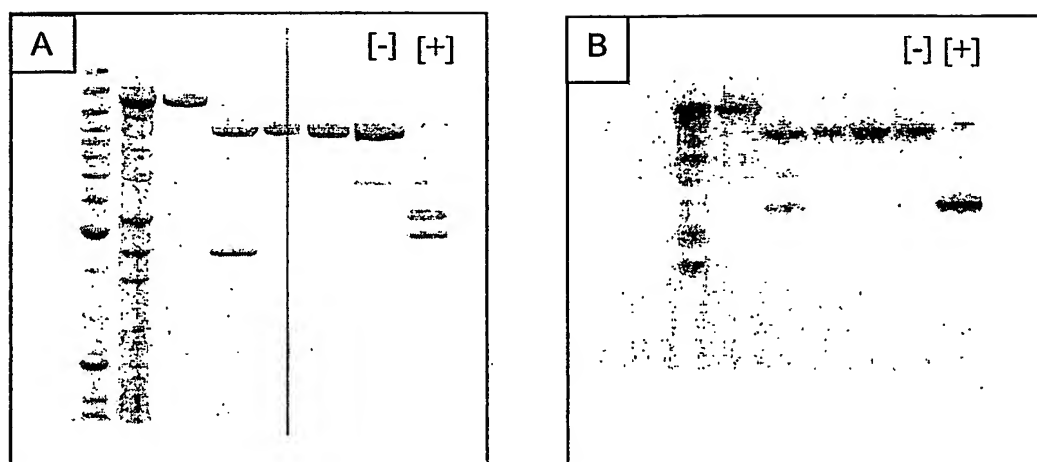
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Figure 4



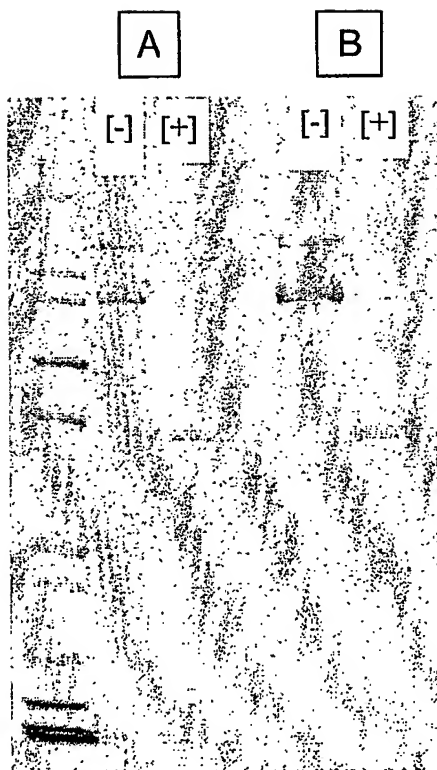
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Figure 5



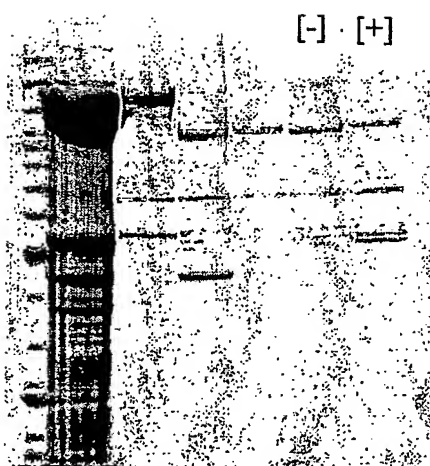
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Figure 6



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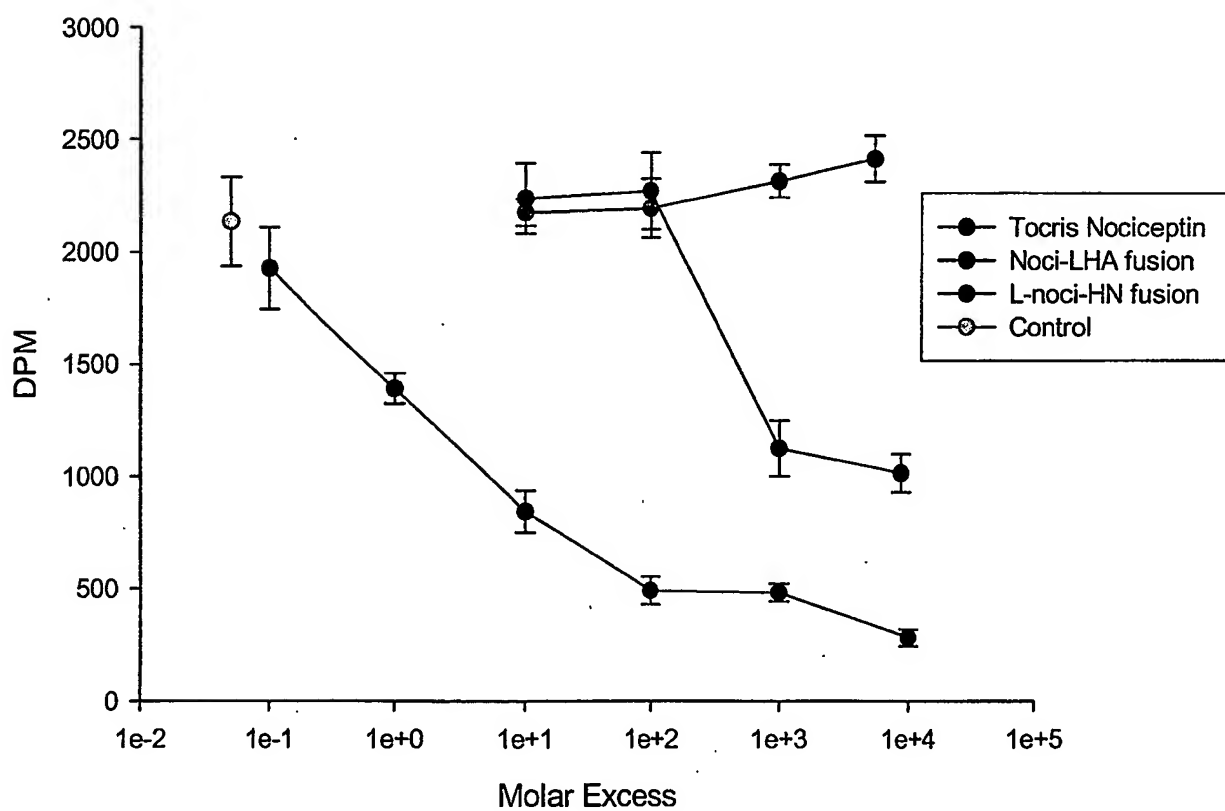
Figure 7



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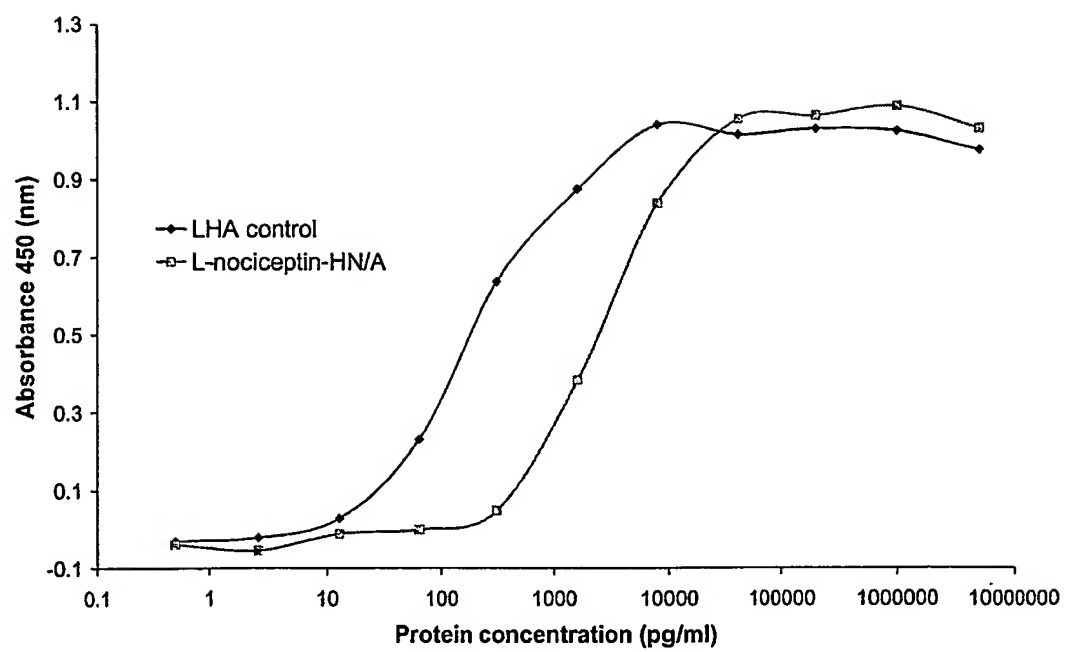
Figure 8

Competition Assay : Nociceptin-LH_N/A Fusions
vs 1nM [³H]-Nociceptin on eDRGs (4°C)



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Figure 9



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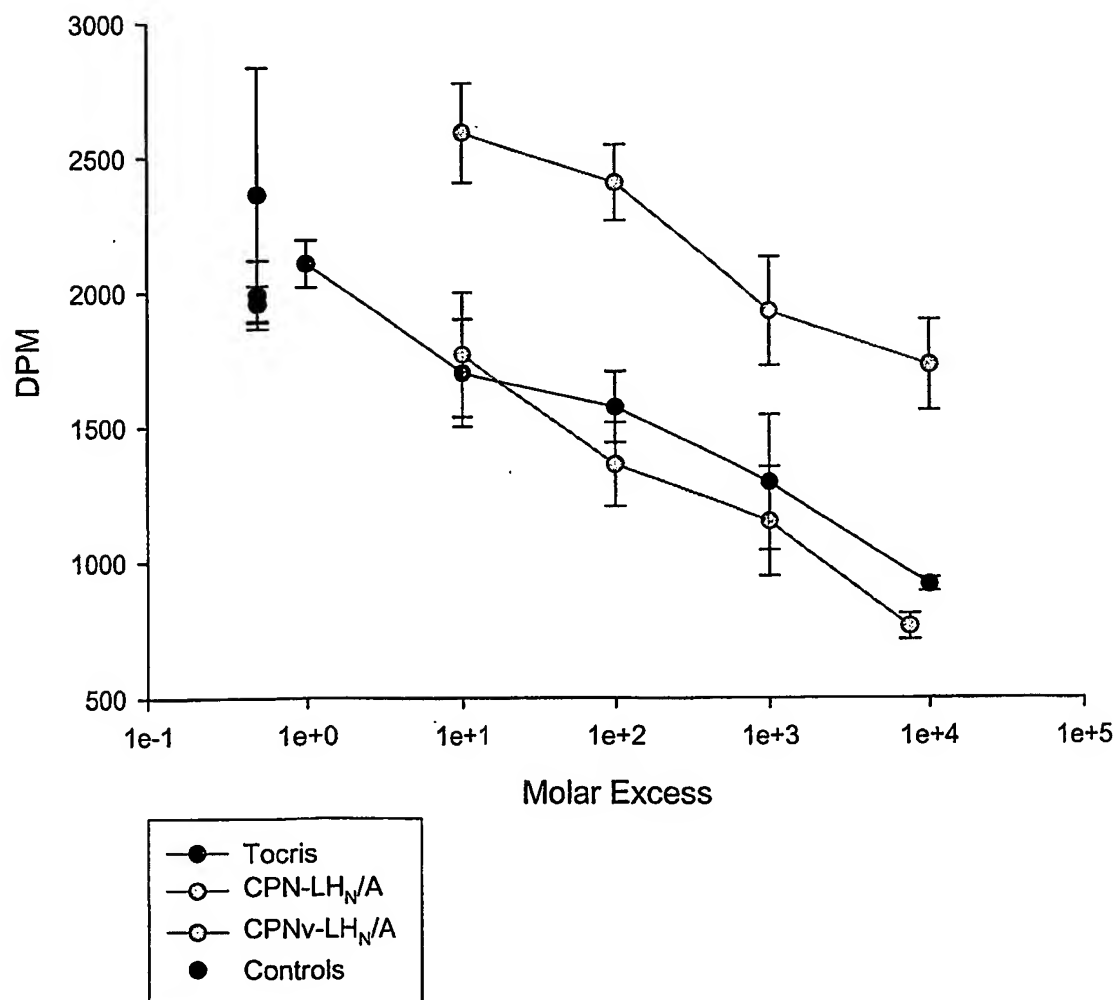
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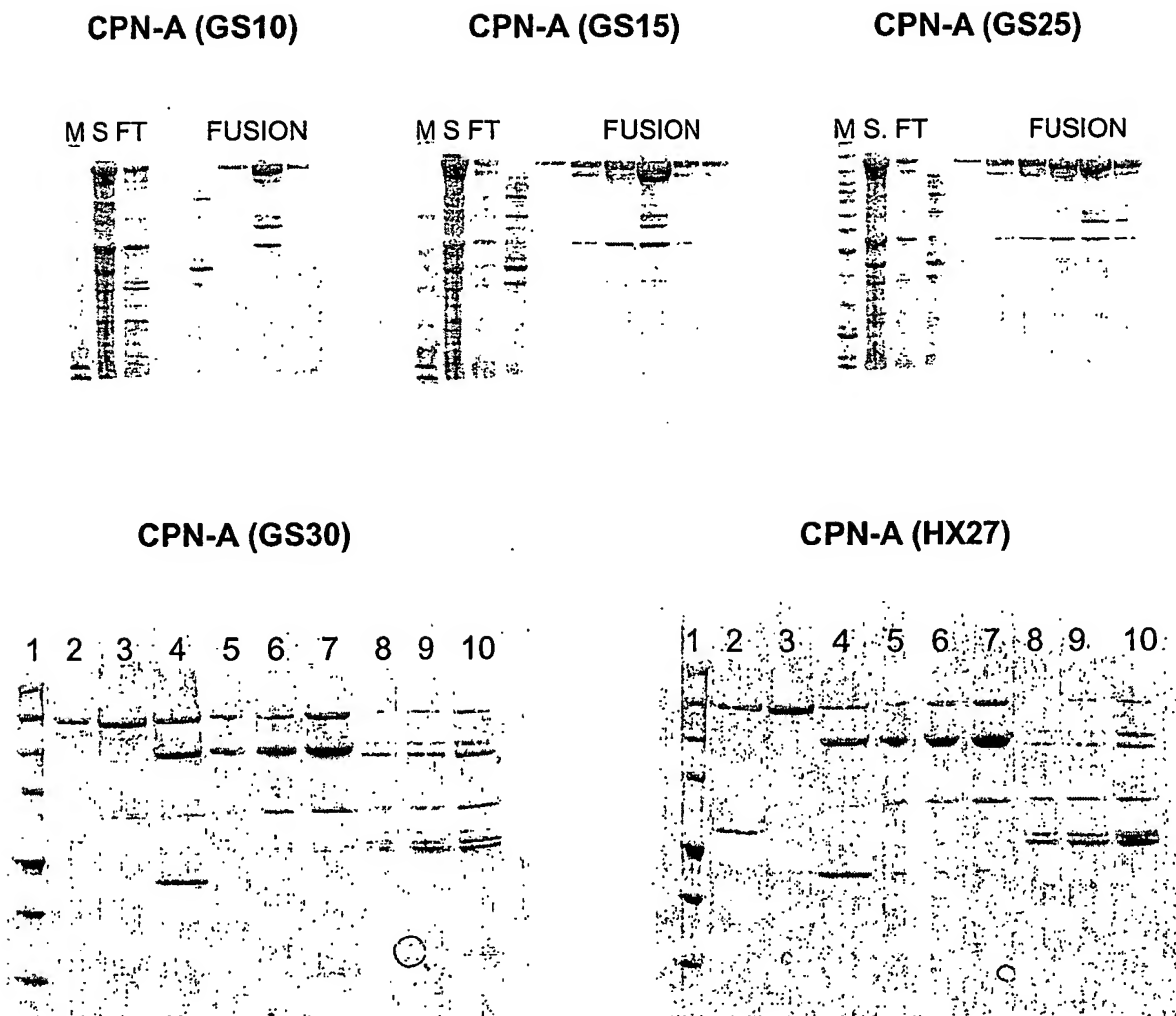
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Competition Assay: CPN fusions vs 1nM [3H] - Nociceptin
on eDRGs for 1 hour at 4°C



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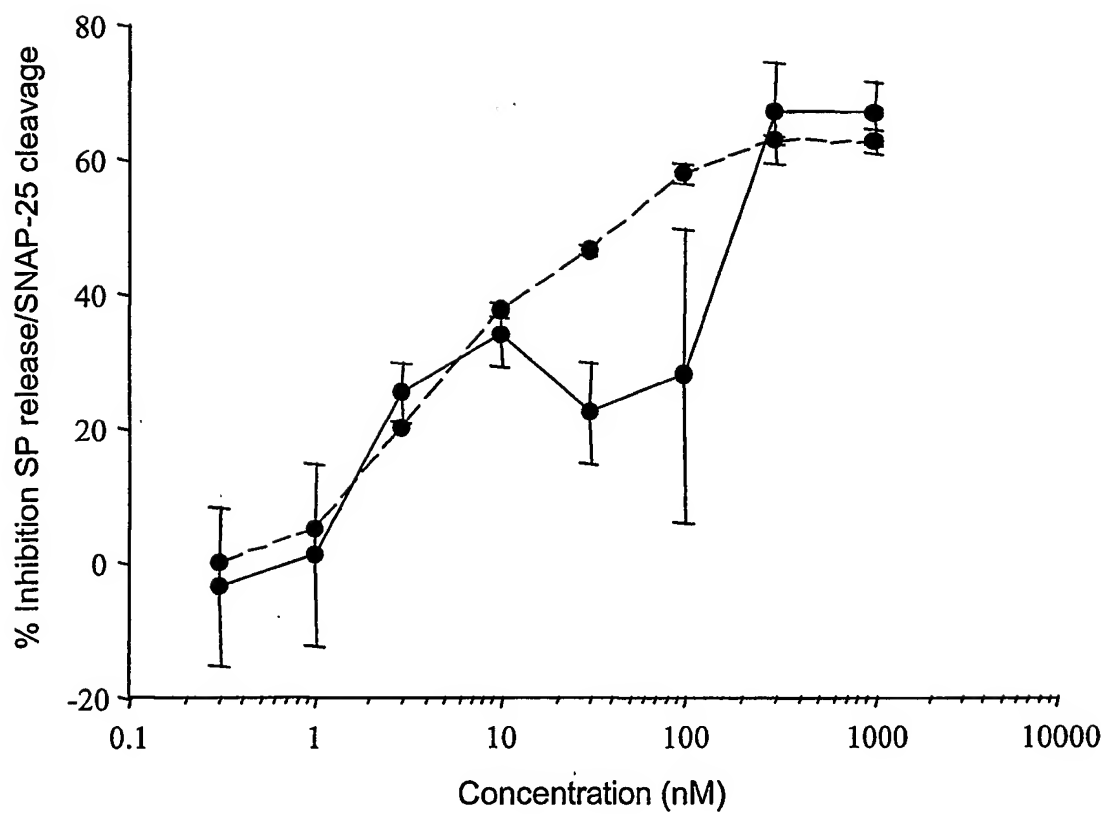
Figure 12



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Figure 13

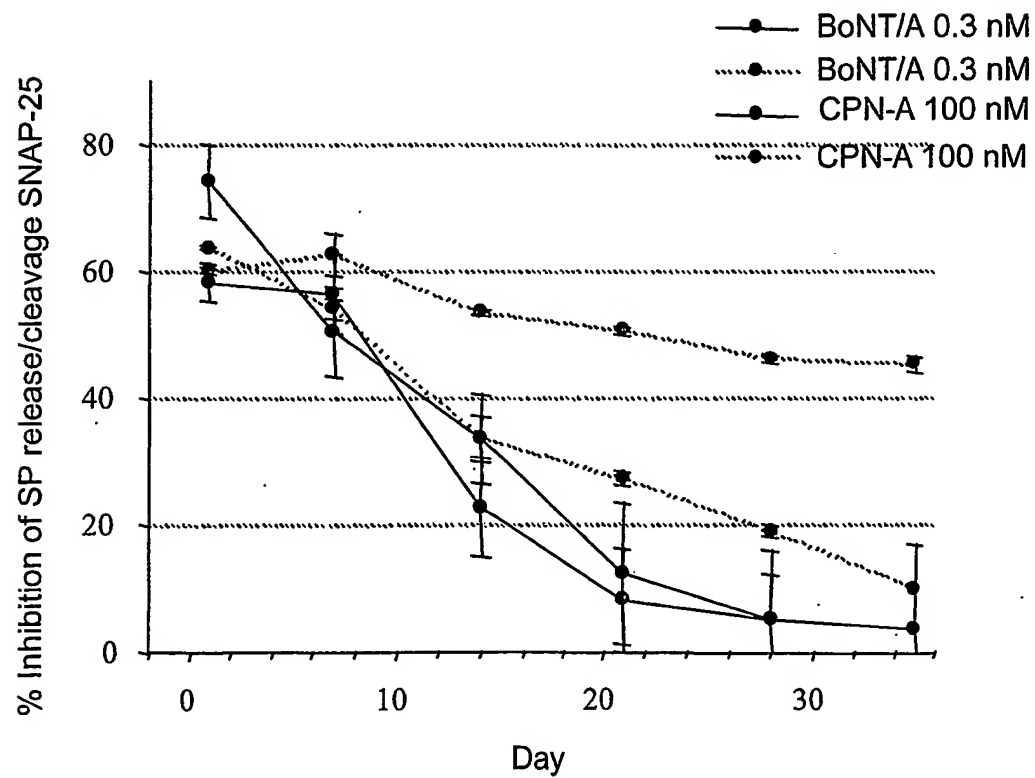
CPN-A on eDRG for 1 Day



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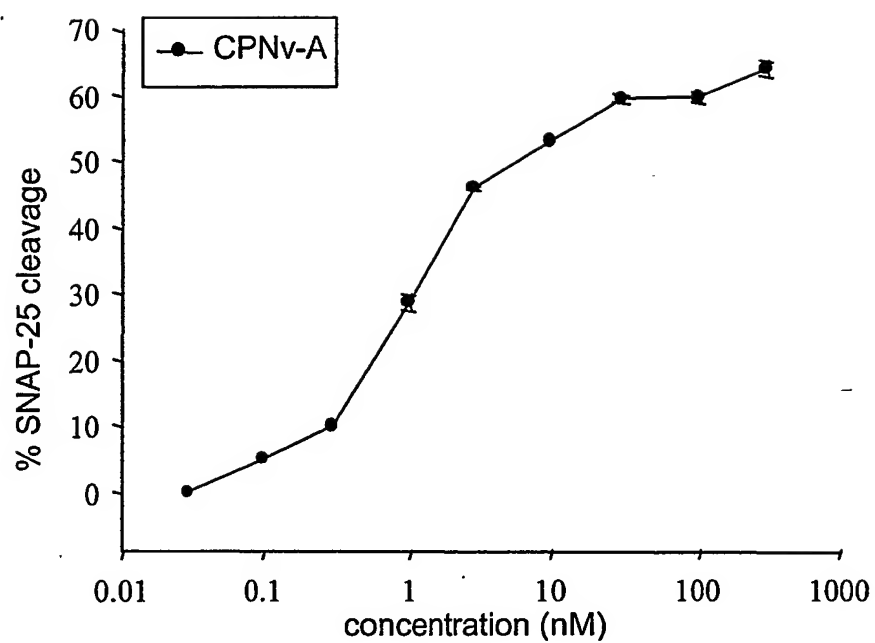
Figure 14

Duration of action following eDRG exposure for 1 Day



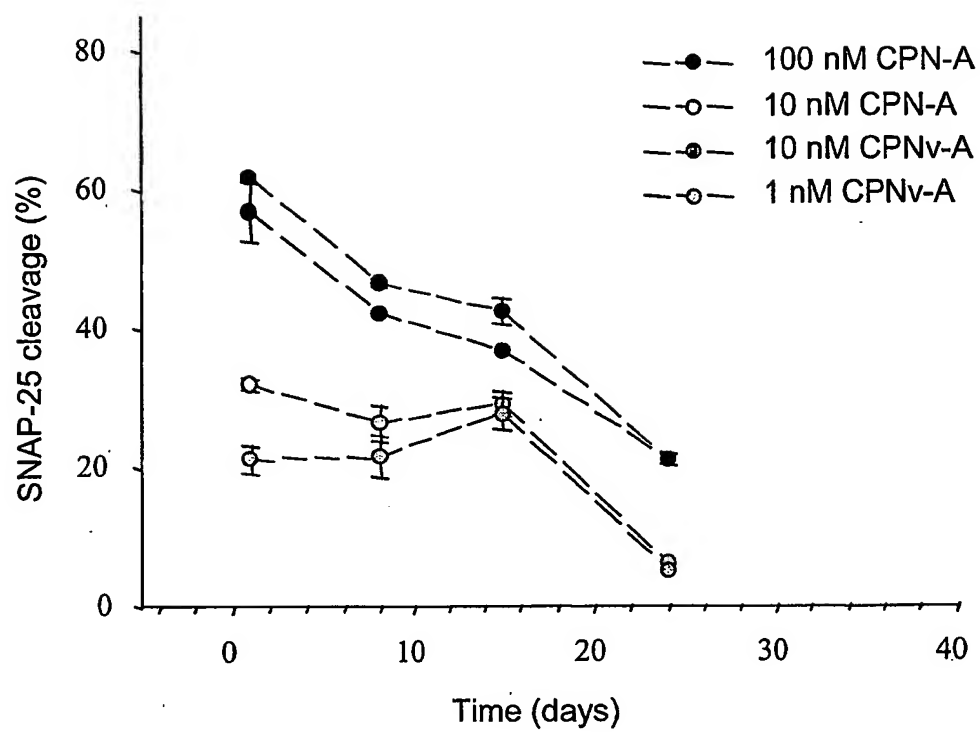
15/32

Figure 15



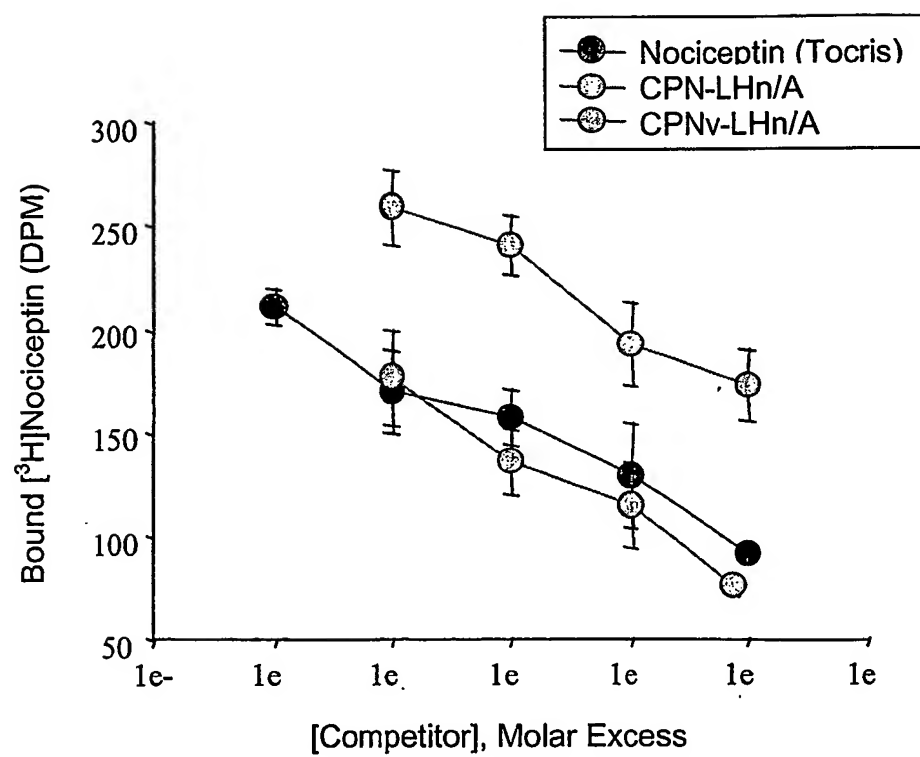
16/32

Figure 16



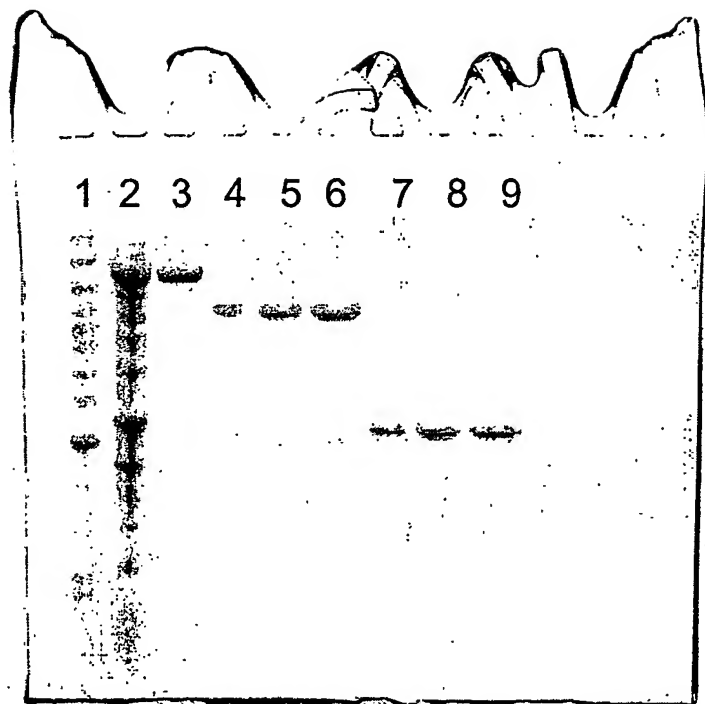
17/32

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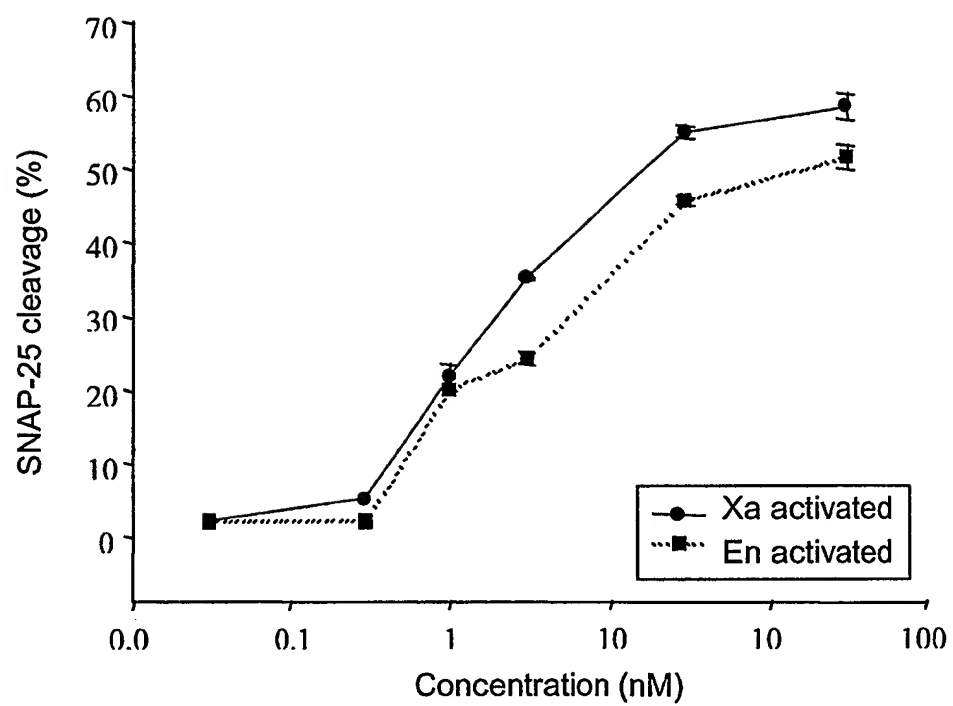
18/32

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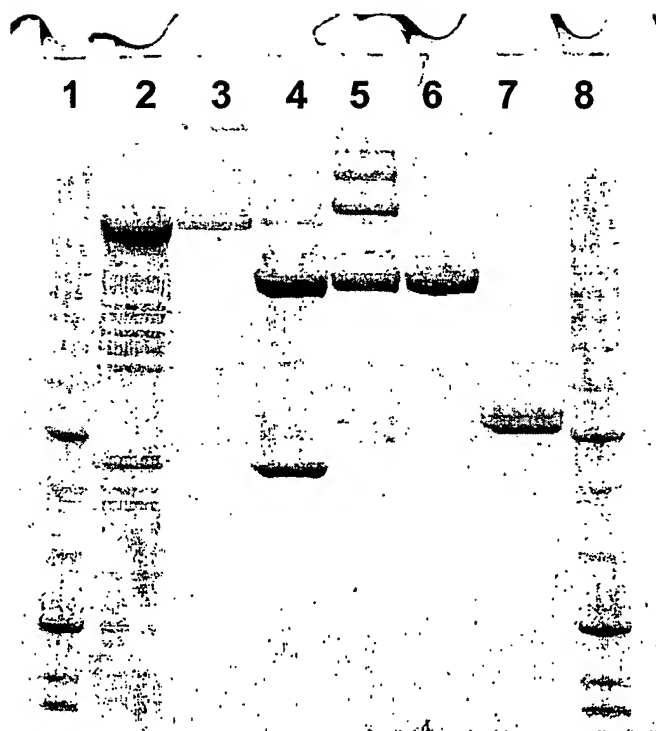
19/32

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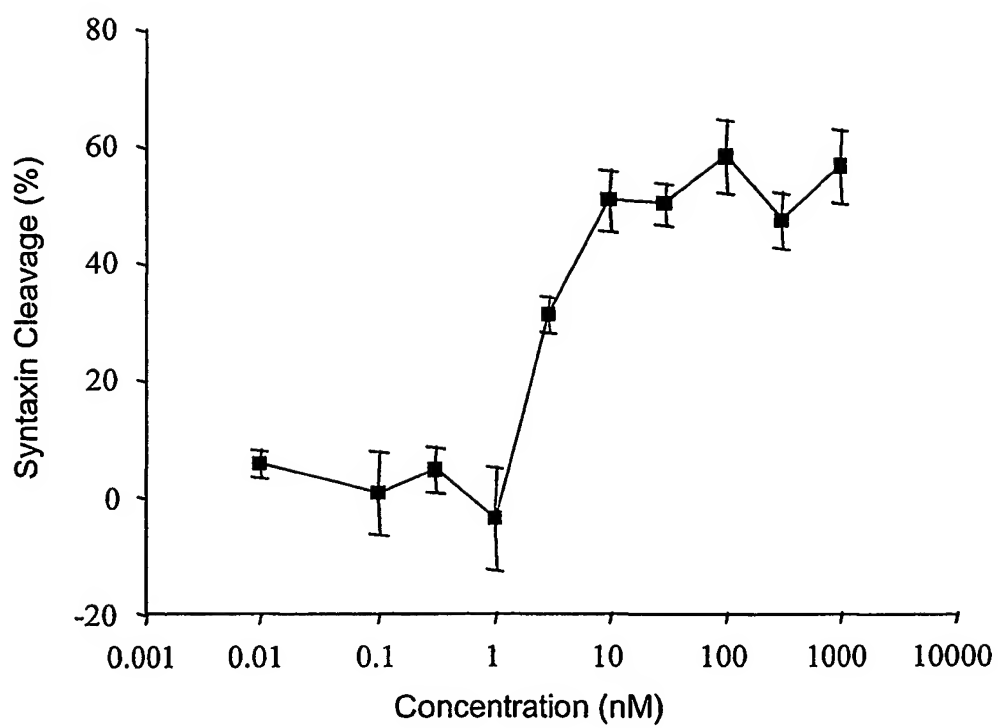
20/32

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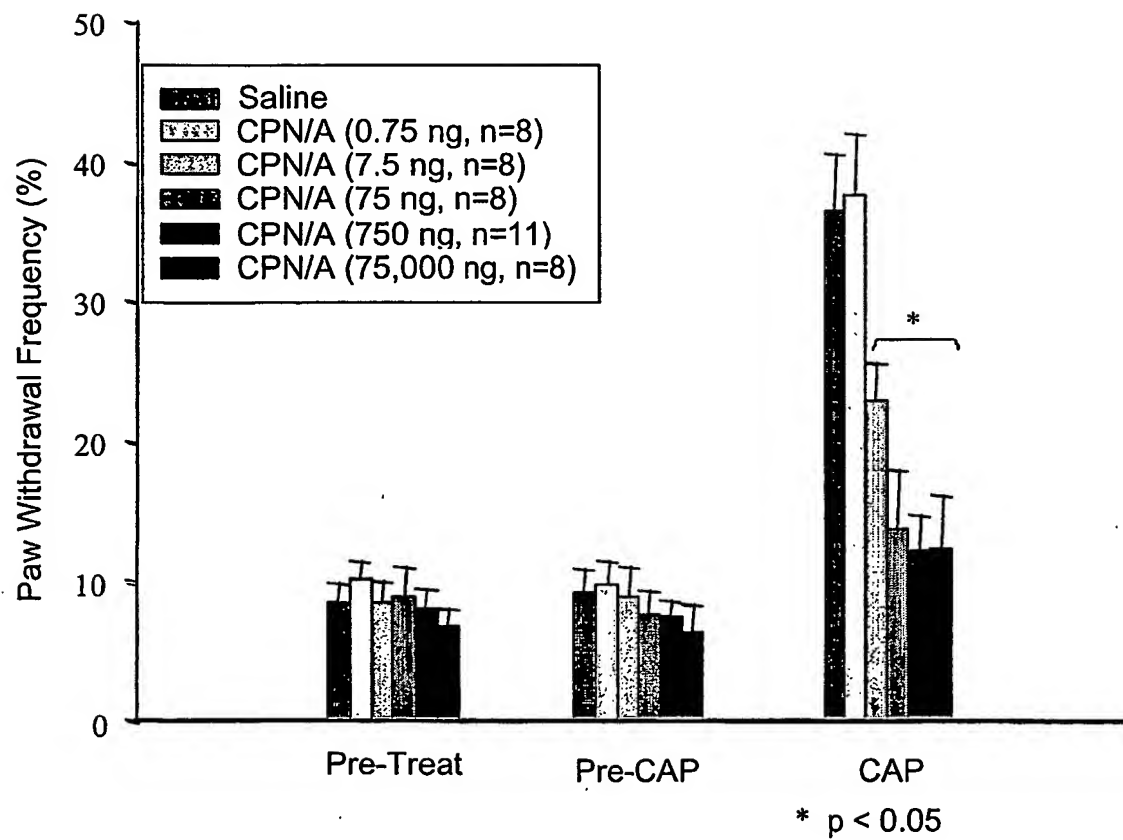
21/32

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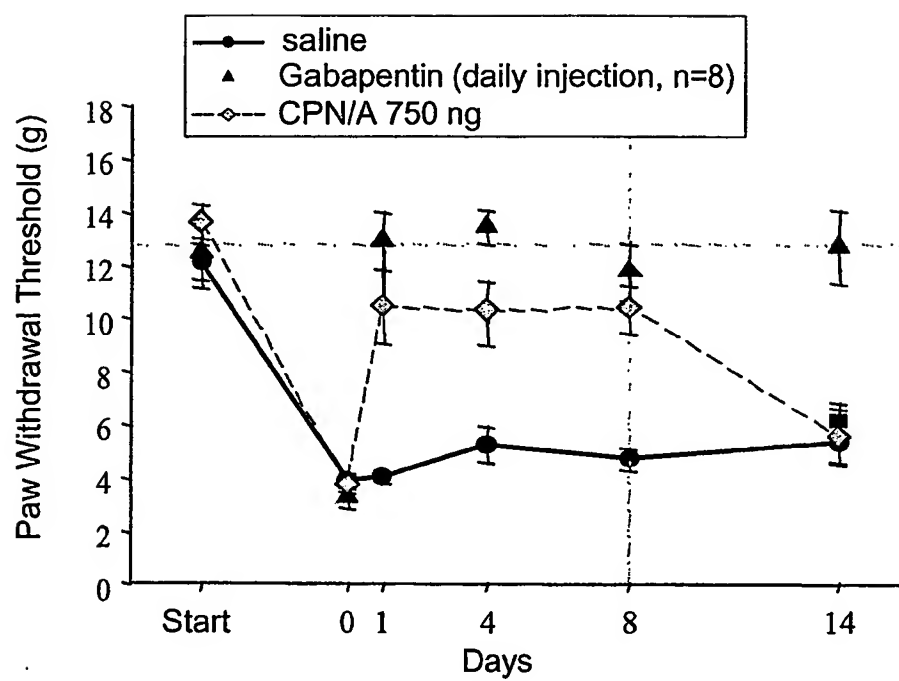
22/32

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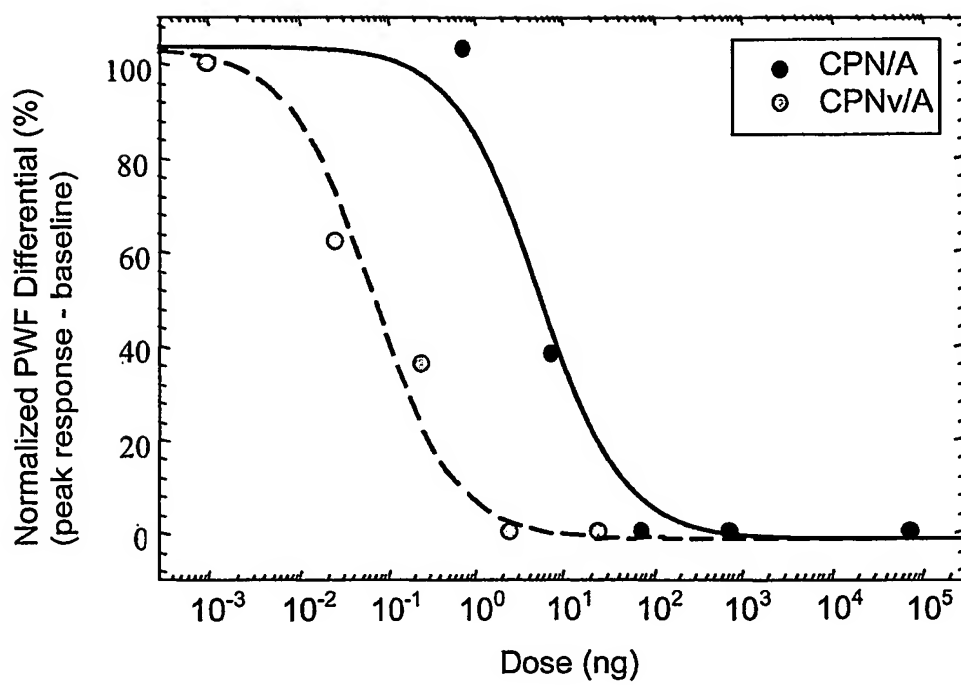
23/32

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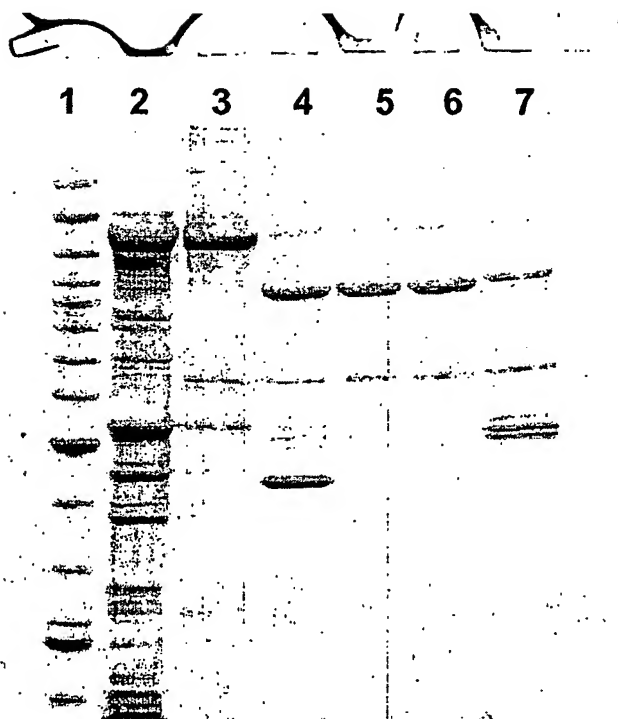
24/32

Figure 24



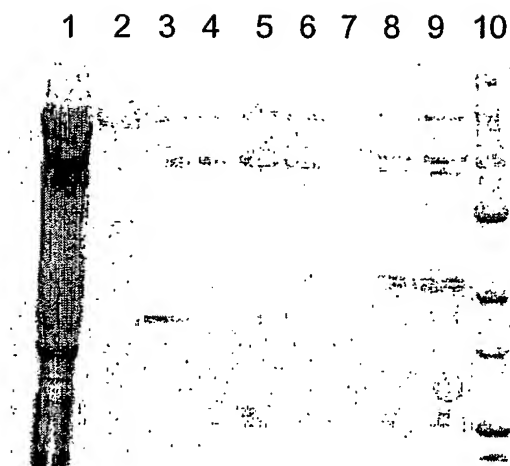
25/32

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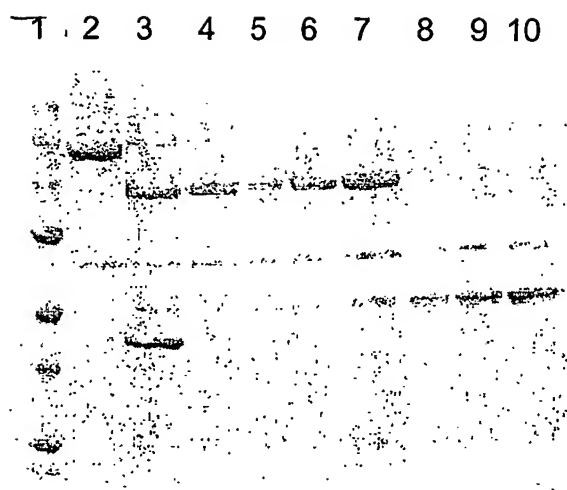
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Figure 26



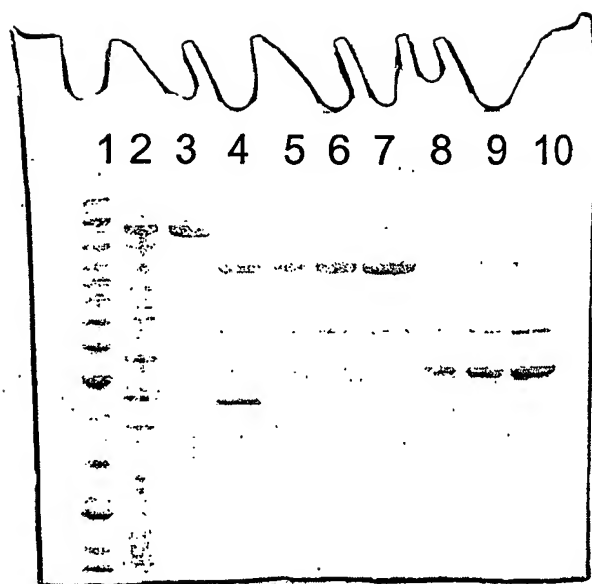
27/32

Figure 27



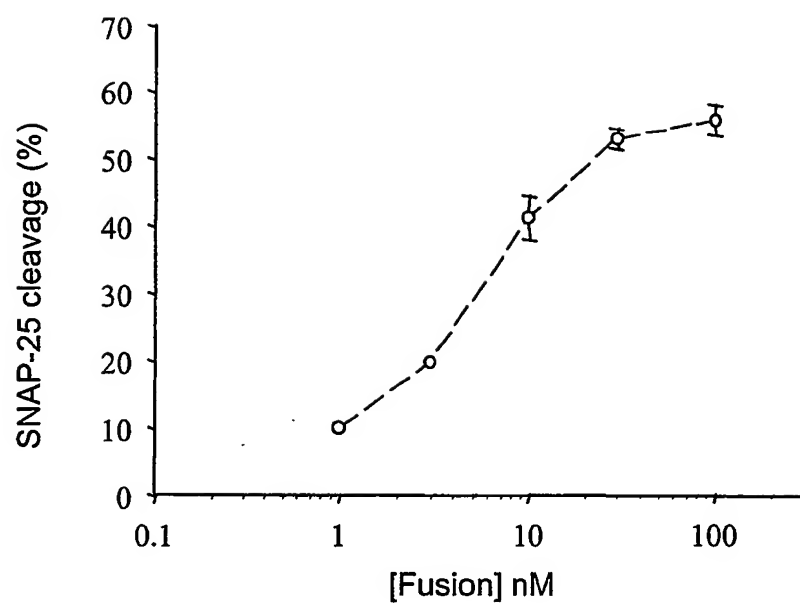
28/32

Figure 28



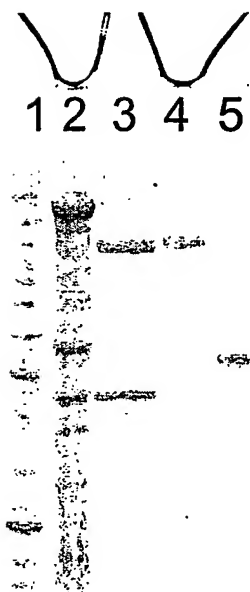
29/32

Figure 29



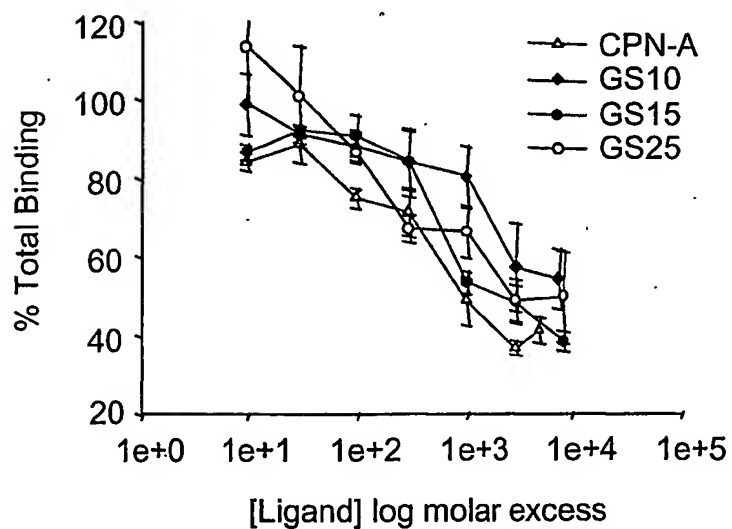
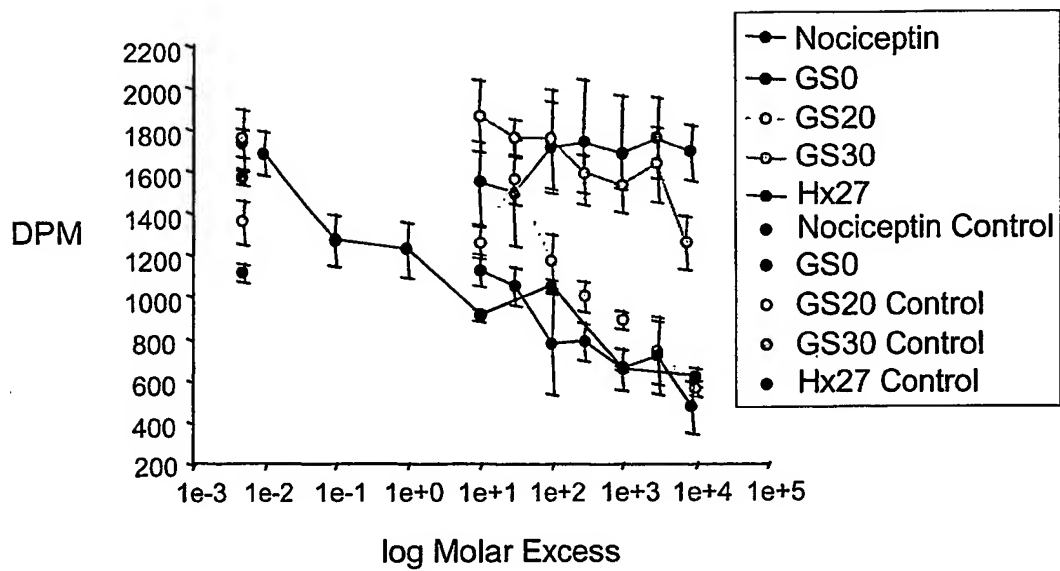
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Figure 30



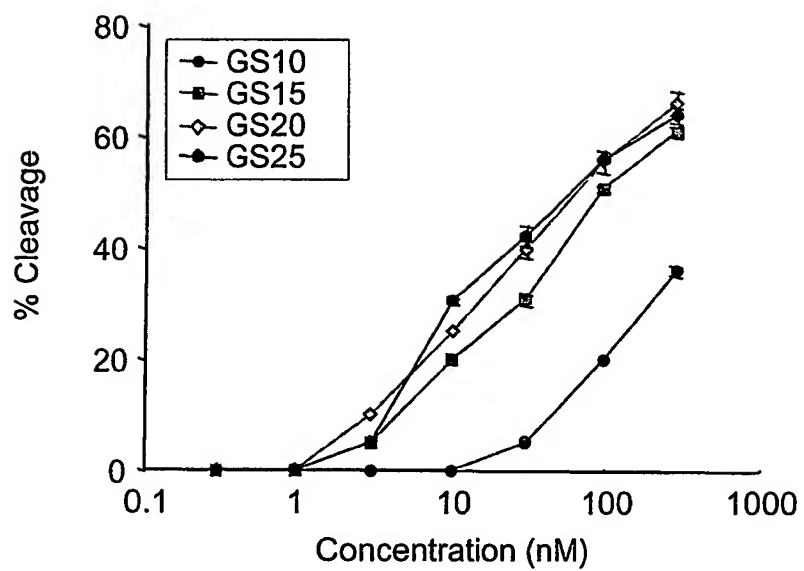
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Figure 31



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Figure 32



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Penn, Charles
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<210> 18
 <211> 899
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 18

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Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Pro Arg Gly Ser

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Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly		
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Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro		
50	55	60
Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg		
65	70	75
Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro Pro Glu		
85	90	95
Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr		
100	105	110
Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu		
115	120	125
Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val		
130	135	140
Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys		
145	150	155
Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr		
165	170	175
Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile		
180	185	190
Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr		
195	200	205
Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe		
210	215	220
Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu		
225	230	235
Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu		
245	250	255
Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn		
260	265	270

Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu
275 280 285

Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys
290 295 300

Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn
305 310 315 320

Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser Ile Val
325 330 335

Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys Glu Lys
340 345 350

Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp Lys Leu
355 360 365

Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr Glu Asp
370 375 380

Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr Leu Asn
385 390 395 400

Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val Asn Tyr
405 410 415

Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala Ala Asn
420 425 430

Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr Lys Leu
435 440 445

Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys Val Asp
450 455 460

Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg Asn Lys
465 470 475 480

Ala Leu Asn Asp Leu Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe
485 490 495

Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu
500 505 510

Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu
 515 520 525

Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro
 530 535 540

Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu
 545 550 555 560

Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu
 565 570 575

Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu
 580 585 590

His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu
 595 600 605

Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys
 610 615 620

Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu
 625 630 635 640

Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr
 645 650 655

Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala
 660 665 670

Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu
 675 680 685

Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala
 690 695 700

Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys
 705 710 715 720

Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu
 725 730 735

Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys
 740 745 750

Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu
755 760 765

Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn
770 775 780

Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp
785 790 795 800

Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile
805 810 815

Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met
820 825 830

Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys
835 840 845

Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly
850 855 860

Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp
865 870 875 880

Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser
885 890 895

Thr Leu Asp

<210> 19
<211> 2706
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

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cagttcaact ataaagaccc agttaacggg gttgacattg cttacatcaa aatcccgaac 180
gctggccaga tgcagccggt aaaggcattc aaaatccaca acaaaatctg gggttatccc 240
gaacgtgata cctttactaa cccggaagaa ggtgacctga acccgccacc ggaagcgaaa 300
caggtgcggg tatcttacta tgactccacc tacctgtcta ccgataacga aaaggacaac 360

tacctgaaag gtgttactaa actgttcgag cgtatttact ccaccgacct gggccgatatg	420
ctgctgacta gcatcgttcg cggatatcccg ttctggggcg gttctaccat cgataccgaa	480
ctgaaagtaa tcgacactaa ctgcatcaac gttattcagc cggacgggtc ctatcgttcc	540
gaagaactga acctggtgat catcggcccg tctgctgata tcatccagtt cgagtgtaaag	600
agctttggtc acgaagttct gaacctcacc cgtaacggct acggttccac tcagtacatc	660
cgtttctctc cggacttcac cttcggtttt gaagaatccc tggaagtaga cacgaaccca	720
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accaacgcgt attacgagat gtccgggtctg gaagtttagct tcgaagaact gcgtactttt	900
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acctccggca aattctctgt agacaagttg aaattcgata aactttacaa aatgctgact	1140
gaaatttaca ccgaagacaa cttcgttaag ttctttaaag ttctgaaccg caaacctat	1200
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tacgatgggt tcaacctgag taacaccaac ctggctgcta attttaacgg ccagaacacg	1320
gaaatcaaca acatgaactt cacaaaactg aaaaacttca ctggctctgt cgagttttac	1380
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aatttcgaca acgagccgga aaacatttct atcgaaaacc tgagctctga tatcatcggc	1680
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 gactag 2706

<210> 20
 <211> 901
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 20

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Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
 35 40 45

Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
 50 55 60

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
 65 70 75 80

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
 85 90 95

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
 100 105 110

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
 115 120 125

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
 130 135 140

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
 145 150 155 160

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
 165 170 175

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
 180 185 190

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
 195 200 205

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
 210 215 220

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 225 230 235 240

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
 245 250 255

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 260 265 270

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
 275 280 285

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 290 295 300

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
 305 310 315 320

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
 325 330 335

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
 340 345 350

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 355 360 365

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 370 375 380

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 385 390 395 400

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 405 410 415

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 420 425 430

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 435 440 445

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 450 455 460

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
 465 470 475 480

Asn Lys Ala Leu Asn Asp Leu Cys Ile Lys Val Asn Asn Trp Asp Leu
 485 490 495

Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly
 500 505 510

Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile
 515 520 525

Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn
 530 535 540

Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly
 545 550 555 560

Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys
 565 570 575

Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu
 580 585 590

Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu
 595 600 605

Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr

610	615	620
Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp		
625	630	635 640
Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser		
	645	650 655
Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly		
	660	665 670
Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly		
	675	680 685
Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu		
	690	695 700
Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala		
705	710	715 720
Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg		
	725	730 735
Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu		
	740	745 750
Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu		
	755	760 765
Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln		
	770	775 780
Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile		
785	790	795 800
Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile		
	805	810 815
Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn		
	820	825 830
Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser		
	835	840 845
Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu		
850	855	860

Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser
 865 870 875 880

Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu
 885 890 895

Leu Ser Thr Leu Asp
 900

<210> 21
 <211> 2691
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 21
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 aaaatctggg ttatcccga acgtgatacc ttactaacc cggaagaagg tgacctgaac 180
 ccgccaccgg aagcgaaaca ggtgccggta tcttactatg actccaccta cctgtctacc 240
 gataacgaaa aggacaacta cctgaaaggt gttactaaac tggtcgagcg tatctactcc 300
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 gacggttcct atcggtccga agaactgaac ctggtgatca tcggcccgtc tgctgatatc 480
 atccagttcg agtgtaagag ctttggtcac gaagttctga acctcaccgg taacggctac 540
 ggttccactc agtacatccg tttctctccg gacttcacct tcggttttga agaatccctg 600
 gaagtagaca cgaaccact gctgggcgct ggtaaattcg caactgatcc tgcggttacc 660
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 cgtgtcttca aagttaacac caacgcgtat tacgagatgt ccggtctgga agttagcttc 780
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 aaatccatcg tgggtaccac tgcttctctc cagtacatga agaacgtttt taaagaaaaa 960
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 ctttacaaaa tgctgactga aatttacacc gaagacaact tcgttaagtt ctttaaagtt 1080
 ctgaaccgca aaacctatct gaacttcgac aaggcagtat tcaaaatcaa catcgtgccg 1140

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aacatcaact tcaacatcga cgatctgtcc tctaaactga acgaatccat caacaaagct 2340
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cgcttttgt cactggcgg tgggggtagt ggcggtggcg gttcgggcgg ggggtgggagc 2640
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<210> 22

<211> 897

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 22

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Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro
20 25 30

Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg
35 40 45

Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro Pro Glu
50 55 60

Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr
65 70 75 80

Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu
85 90 95

Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val
100 105 110

Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys
115 120 125

Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr
130 135 140

Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile
145 150 155 160

Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr
165 170 175

Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe
180 185 190

Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu
195 200 205

Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu
210 215 220

Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn
225 230 235 240

Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu
245 250 255

Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys
260 265 270

Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn
275 280 285

Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser Ile Val
290 295 300

Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys Glu Lys
305 310 315 320

Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp Lys Leu
325 330 335

Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr Glu Asp
340 345 350

Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr Leu Asn
355 360 365

Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val Asn Tyr
370 375 380

Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala Ala Asn
385 390 395 400

Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr Lys Leu
405 410 415

Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys Val Asp
420 425 430

Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg Asn Lys
435 440 445

Ala Leu Asn Asp Leu Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe
450 455 460

Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu
465 470 475 480

Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu
 485 490 495

Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro
 500 505 510

Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu
 515 520 525

Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu
 530 535 540

Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu
 545 550 555 560

His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu
 565 570 575

Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys
 580 585 590

Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu
 595 600 605

Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr
 610 615 620

Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala
 625 630 635 640

Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu
 645 650 655

Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala
 660 665 670

Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys
 675 680 685

Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu
 690 695 700

Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys
 705 710 715 720

Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu

725	730	735
Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn 740 745 750		
Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp 755 760 765		
Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile 770 775 780		
Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met 785 790 795 800		
Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys 805 810 815		
Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly 820 825 830		
Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp 835 840 845		
Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser 850 855 860		
Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser 865 870 875 880		
Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Leu Ala Asn 885 890 895		

Gln

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 <211> 2676
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

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 ggaaatatat gggtaatacc tgatagattt tcaagaaatt ctaatccaaa tttaaataaa 180

cctcctcgag ttacaagccc taaaagtggg tattatgatc ctaattatth gagtactgat	240
tctgacaaaag atacatththt aaaagaaatt ataaagttat ttaaaagaat taattctaga	300
gaaataggag aagaattaat atatagactt tcgacagata taccctthtcc tgggaataac	360
aatactccaa ttaatacctt tgatthtgat gtagatthta acagtgttga tgttaaaact	420
agacaaggta acaactgggt taaaactggg agcataaatc ctagtgtht aataactgga	480
cctagagaaa acattataga tccagaaact tctacgttht aattaactaa caatacctth	540
gcggcacaaag aaggatthtg tgctthtca ataathtcaa taccacctag atthtatgcta	600
acatatagta atgcaactaa tgatgtagga gagggtagat thtctaagtc tgaatthtgc	660
atggatccaa tactaaththt aatgcatgaa cttaatcatg caatgcataa thtatatgga	720
atagctatac caaatgatca acaaththtca tctgtaacta gtaaththt thattctcaa	780
tataatgtga aattagagta tgcagaaata tatgcathtg gaggtccaac tatagacctt	840
attcctaaaa gtgcaaggaa ataththtgag gaaaaggcat tggattatta tagatctata	900
gctaaaagac ttaatagtat aactactgca aatcctthcaa gctthtaata atatataggg	960
gaatataaac agaaacttat tagaaagtat agattcgtag tagaatcttc aggtgaagtt	1020
acagtaaatc gtaataagtt tgthtgagtha tataatgaac ttacacaaat atthacagaa	1080
thtaactacg ctaaaatata taatgtacaa aataggaaaa tatatctthc aaatgtatat	1140
actccggtta cggcgaatat attagacgat aatgthtatg atatacaaaa tggatthta	1200
atacctaaaa gtaaththaa tgtactatth atgggtcaaa atthtatctg aaatccagca	1260
thtaagaaaag tcaatcctga aaatatgctt ththththta caaaaththg tcataaagca	1320
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actgacttac cctthtatagg tgatattagt gatgthtaaa ctgatataat thtaagaaaa	1440
gatattaatg aagaaactga agthtatata tatccggaca atgththcagt agatcaagtt	1500
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tgggcaaatg atgtagthga agaththtact acaaatatth taagaaaaaga tacattagat	1860
aaaatatcag atgtatcagc thththtccc tatataggac ccgcattaaa tataagtaat	1920
tctgtaagaa gaggaathth tactgaagca thtgagthta ctggtgtaac ththththta	1980

gaagcatttc ctgaatttac aatacctgca cttggtgcat ttgtgattta tagtaagggtt 2040
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 aaaatagatt tagaatataa aaaatattca ggaagtgata aagaaaatat aaaaagtcaa 2280
 gttgaaaatt taaaaaatag ttttagatgta aaaatttcgg aagcaatgaa taatataaat 2340
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 gatgaattaa atgagtttga tcgaaatact aaagcaaaat taattaatct tatagatagt 2460
 cataatatta ttctagttgg tgaagtagat aaattaaaag caaaagtaaa taatagcttt 2520
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 <211> 892
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 24

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Lys Asn Ile Leu Tyr Leu Asp Thr His Leu Asn Thr Leu Ala Asn Glu
20 25 30

Pro Glu Lys Ala Phe Arg Ile Thr Gly Asn Ile Trp Val Ile Pro Asp
35 40 45

Arg Phe Ser Arg Asn Ser Asn Pro Asn Leu Asn Lys Pro Pro Arg Val
50 55 60

Thr Ser Pro Lys Ser Gly Tyr Tyr Asp Pro Asn Tyr Leu Ser Thr Asp
65 70 75 80

Ser Asp Lys Asp Thr Phe Leu Lys Glu Ile Ile Lys Leu Phe Lys Arg
85 90 95

Ile Asn Ser Arg Glu Ile Gly Glu Glu Leu Ile Tyr Arg Leu Ser Thr
100 105 110

Asp Ile Pro Phe Pro Gly Asn Asn Asn Thr Pro Ile Asn Thr Phe Asp
 115 120 125

Phe Asp Val Asp Phe Asn Ser Val Asp Val Lys Thr Arg Gln Gly Asn
 130 135 140

Asn Trp Val Lys Thr Gly Ser Ile Asn Pro Ser Val Ile Ile Thr Gly
 145 150 155 160

Pro Arg Glu Asn Ile Ile Asp Pro Glu Thr Ser Thr Phe Lys Leu Thr
 165 170 175

Asn Asn Thr Phe Ala Ala Gln Glu Gly Phe Gly Ala Leu Ser Ile Ile
 180 185 190

Ser Ile Ser Pro Arg Phe Met Leu Thr Tyr Ser Asn Ala Thr Asn Asp
 195 200 205

Val Gly Glu Gly Arg Phe Ser Lys Ser Glu Phe Cys Met Asp Pro Ile
 210 215 220

Leu Ile Leu Met His Glu Leu Asn His Ala Met His Asn Leu Tyr Gly
 225 230 235 240

Ile Ala Ile Pro Asn Asp Gln Thr Ile Ser Ser Val Thr Ser Asn Ile
 245 250 255

Phe Tyr Ser Gln Tyr Asn Val Lys Leu Glu Tyr Ala Glu Ile Tyr Ala
 260 265 270

Phe Gly Gly Pro Thr Ile Asp Leu Ile Pro Lys Ser Ala Arg Lys Tyr
 275 280 285

Phe Glu Glu Lys Ala Leu Asp Tyr Tyr Arg Ser Ile Ala Lys Arg Leu
 290 295 300

Asn Ser Ile Thr Thr Ala Asn Pro Ser Ser Phe Asn Lys Tyr Ile Gly
 305 310 315 320

Glu Tyr Lys Gln Lys Leu Ile Arg Lys Tyr Arg Phe Val Val Glu Ser
 325 330 335

Ser Gly Glu Val Thr Val Asn Arg Asn Lys Phe Val Glu Leu Tyr Asn
 340 345 350

Glu Leu Thr Gln Ile Phe Thr Glu Phe Asn Tyr Ala Lys Ile Tyr Asn
 355 360 365

Val Gln Asn Arg Lys Ile Tyr Leu Ser Asn Val Tyr Thr Pro Val Thr
 370 375 380

Ala Asn Ile Leu Asp Asp Asn Val Tyr Asp Ile Gln Asn Gly Phe Asn
 385 390 395 400

Ile Pro Lys Ser Asn Leu Asn Val Leu Phe Met Gly Gln Asn Leu Ser
 405 410 415

Arg Asn Pro Ala Leu Arg Lys Val Asn Pro Glu Asn Met Leu Tyr Leu
 420 425 430

Phe Thr Lys Phe Cys His Lys Ala Ile Asp Gly Arg Ser Leu Tyr Asn
 435 440 445

Lys Thr Leu Asp Cys Arg Glu Leu Leu Val Lys Asn Thr Asp Leu Pro
 450 455 460

Phe Ile Gly Asp Ile Ser Asp Val Lys Thr Asp Ile Phe Leu Arg Lys
 465 470 475 480

Asp Ile Asn Glu Glu Thr Glu Val Ile Tyr Tyr Pro Asp Asn Val Ser
 485 490 495

Val Asp Gln Val Ile Leu Ser Lys Asn Thr Ser Glu His Gly Gln Leu
 500 505 510

Asp Leu Leu Tyr Pro Ser Ile Asp Ser Glu Ser Glu Ile Leu Pro Gly
 515 520 525

Glu Asn Gln Val Phe Tyr Asp Asn Arg Thr Gln Asn Val Asp Tyr Leu
 530 535 540

Asn Ser Tyr Tyr Tyr Leu Glu Ser Gln Lys Leu Ser Asp Asn Val Glu
 545 550 555 560

Asp Phe Thr Phe Thr Arg Ser Ile Glu Glu Ala Leu Asp Asn Ser Ala
 565 570 575

Lys Val Tyr Thr Tyr Phe Pro Thr Leu Ala Asn Lys Val Asn Ala Gly
 580 585 590

Val Gln Gly Gly Leu Phe Leu Met Trp Ala Asn Asp Val Val Glu Asp
595 600 605

Phe Thr Thr Asn Ile Leu Arg Lys Asp Thr Leu Asp Lys Ile Ser Asp
610 615 620

Val Ser Ala Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Ser Asn
625 630 635 640

Ser Val Arg Arg Gly Asn Phe Thr Glu Ala Phe Ala Val Thr Gly Val
645 650 655

Thr Ile Leu Leu Glu Ala Phe Pro Glu Phe Thr Ile Pro Ala Leu Gly
660 665 670

Ala Phe Val Ile Tyr Ser Lys Val Gln Glu Arg Asn Glu Ile Ile Lys
675 680 685

Thr Ile Asp Asn Cys Leu Glu Gln Arg Ile Lys Arg Trp Lys Asp Ser
690 695 700

Tyr Glu Trp Met Met Gly Thr Trp Leu Ser Arg Ile Ile Thr Gln Phe
705 710 715 720

Asn Asn Ile Ser Tyr Gln Met Tyr Asp Ser Leu Asn Tyr Gln Ala Gly
725 730 735

Ala Ile Lys Ala Lys Ile Asp Leu Glu Tyr Lys Lys Tyr Ser Gly Ser
740 745 750

Asp Lys Glu Asn Ile Lys Ser Gln Val Glu Asn Leu Lys Asn Ser Leu
755 760 765

Asp Val Lys Ile Ser Glu Ala Met Asn Asn Ile Asn Lys Phe Ile Arg
770 775 780

Glu Cys Ser Val Thr Tyr Leu Phe Lys Asn Met Leu Pro Lys Val Ile
785 790 795 800

Asp Glu Leu Asn Glu Phe Asp Arg Asn Thr Lys Ala Lys Leu Ile Asn
805 810 815

Leu Ile Asp Ser His Asn Ile Ile Leu Val Gly Glu Val Asp Lys Leu
820 825 830

Lys Ala Lys Val Asn Asn Ser Phe Gln Asn Thr Ile Pro Phe Asn Ile

835		840		845
Phe Ser Tyr Thr Asn Asn Ser Leu Leu Lys Asp Ile Ile Asn Glu Tyr				
850		855		860
Phe Asn Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly				
865		870		880
Ser Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala				
	885		890	

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 <211> 2712
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 25
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 ataacaatta acaacttta ttattcagat cctgttgata ataaaaatat tttatattta 180
 gatactcatt taaatacact agctaatac cctgaaaaag cctttcgcac tacaggaaat 240
 atatgggtaa tacctgatag attttcaaga aattctaata caaatttaaa taaacctcct 300
 cgagttacaa gccctaaaag tgggttattat gatcctaatt atttgagtac tgattctgac 360
 aaagatacat ttttaaaaga aattataaag ttatttaaaa gaattaattc tagagaaata 420
 ggagaagaat taatatatag actttcgaca gatataacct ttcctgggaa taacaatact 480
 ccaattaata cctttgattt tgatgtagat tttaacagtg ttgatgttaa aactagacaa 540
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 gaaaacatta tagatccaga aacttctacg tttaaattaa ctaacaatac ctttgcgga 660
 caagaaggat ttggtgcttt atcaataatt tcaatatcac ctagatttat gctaacatat 720
 agtaatgcaa ctaataatgt agtagagggt agattttcta agtctgaatt ttgcatggat 780
 ccaatactaa ttttaatgca tgaacttaat catgcaatgc ataatttata tggaatagct 840
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 aaaagtgcga ggaaatattt tgaggaaaag gcattggatt attatagatc tatagctaaa 1020
 agacttaata gtataactac tgcaaatcct tcaagcttta ataaatatat aggggaatat 1080
 aaacagaaac ttattagaaa gtatagattc gtagtagaat cttcagggtga agttacagta 1140

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attattctag ttggtgaagt agataaatta aaagcaaaag taaataatag ctttcaaaat 2640
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gaatatttca at 2712

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<210> 26

<211> 904

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 26

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Gly Ser Pro Arg Gly Ser Met Pro Ile Thr Ile Asn Asn Phe Asn Tyr
 35 40 45

Ser Asp Pro Val Asp Asn Lys Asn Ile Leu Tyr Leu Asp Thr His Leu
 50 55 60

Asn Thr Leu Ala Asn Glu Pro Glu Lys Ala Phe Arg Ile Thr Gly Asn
 65 70 75 80

Ile Trp Val Ile Pro Asp Arg Phe Ser Arg Asn Ser Asn Pro Asn Leu
 85 90 95

Asn Lys Pro Pro Arg Val Thr Ser Pro Lys Ser Gly Tyr Tyr Asp Pro
 100 105 110

Asn Tyr Leu Ser Thr Asp Ser Asp Lys Asp Thr Phe Leu Lys Glu Ile
 115 120 125

Ile Lys Leu Phe Lys Arg Ile Asn Ser Arg Glu Ile Gly Glu Glu Leu
 130 135 140

Ile Tyr Arg Leu Ser Thr Asp Ile Pro Phe Pro Gly Asn Asn Asn Thr
 145 150 155 160

Pro Ile Asn Thr Phe Asp Phe Asp Val Asp Phe Asn Ser Val Asp Val
 165 170 175

Lys Thr Arg Gln Gly Asn Asn Trp Val Lys Thr Gly Ser Ile Asn Pro
 180 185 190

Ser Val Ile Ile Thr Gly Pro Arg Glu Asn Ile Ile Asp Pro Glu Thr
 195 200 205

Ser Thr Phe Lys Leu Thr Asn Asn Thr Phe Ala Ala Gln Glu Gly Phe
 210 215 220

Gly Ala Leu Ser Ile Ile Ser Ile Ser Pro Arg Phe Met Leu Thr Tyr
225 230 235 240

Ser Asn Ala Thr Asn Asp Val Gly Glu Gly Arg Phe Ser Lys Ser Glu
245 250 255

Phe Cys Met Asp Pro Ile Leu Ile Leu Met His Glu Leu Asn His Ala
260 265 270

Met His Asn Leu Tyr Gly Ile Ala Ile Pro Asn Asp Gln Thr Ile Ser
275 280 285

Ser Val Thr Ser Asn Ile Phe Tyr Ser Gln Tyr Asn Val Lys Leu Glu
290 295 300

Tyr Ala Glu Ile Tyr Ala Phe Gly Gly Pro Thr Ile Asp Leu Ile Pro
305 310 315 320

Lys Ser Ala Arg Lys Tyr Phe Glu Glu Lys Ala Leu Asp Tyr Tyr Arg
325 330 335

Ser Ile Ala Lys Arg Leu Asn Ser Ile Thr Thr Ala Asn Pro Ser Ser
340 345 350

Phe Asn Lys Tyr Ile Gly Glu Tyr Lys Gln Lys Leu Ile Arg Lys Tyr
355 360 365

Arg Phe Val Val Glu Ser Ser Gly Glu Val Thr Val Asn Arg Asn Lys
370 375 380

Phe Val Glu Leu Tyr Asn Glu Leu Thr Gln Ile Phe Thr Glu Phe Asn
385 390 395 400

Tyr Ala Lys Ile Tyr Asn Val Gln Asn Arg Lys Ile Tyr Leu Ser Asn
405 410 415

Val Tyr Thr Pro Val Thr Ala Asn Ile Leu Asp Asp Asn Val Tyr Asp
420 425 430

Ile Gln Asn Gly Phe Asn Ile Pro Lys Ser Asn Leu Asn Val Leu Phe
435 440 445

Met Gly Gln Asn Leu Ser Arg Asn Pro Ala Leu Arg Lys Val Asn Pro
450 455 460

Glu Asn Met Leu Tyr Leu Phe Thr Lys Phe Cys His Lys Ala Ile Asp

465		470		475		480
Gly Arg Ser Leu Tyr Asn Lys Thr Leu Asp Cys Arg Glu Leu Leu Val						
		485		490		495
Lys Asn Thr Asp Leu Pro Phe Ile Gly Asp Ile Ser Asp Val Lys Thr						
		500		505		510
Asp Ile Phe Leu Arg Lys Asp Ile Asn Glu Glu Thr Glu Val Ile Tyr						
		515		520		525
Tyr Pro Asp Asn Val Ser Val Asp Gln Val Ile Leu Ser Lys Asn Thr						
		530		535		540
Ser Glu His Gly Gln Leu Asp Leu Leu Tyr Pro Ser Ile Asp Ser Glu						
		545		550		555
Ser Glu Ile Leu Pro Gly Glu Asn Gln Val Phe Tyr Asp Asn Arg Thr						
		565		570		575
Gln Asn Val Asp Tyr Leu Asn Ser Tyr Tyr Tyr Leu Glu Ser Gln Lys						
		580		585		590
Leu Ser Asp Asn Val Glu Asp Phe Thr Phe Thr Arg Ser Ile Glu Glu						
		595		600		605
Ala Leu Asp Asn Ser Ala Lys Val Tyr Thr Tyr Phe Pro Thr Leu Ala						
		610		615		620
Asn Lys Val Asn Ala Gly Val Gln Gly Gly Leu Phe Leu Met Trp Ala						
		625		630		635
Asn Asp Val Val Glu Asp Phe Thr Thr Asn Ile Leu Arg Lys Asp Thr						
		645		650		655
Leu Asp Lys Ile Ser Asp Val Ser Ala Ile Ile Pro Tyr Ile Gly Pro						
		660		665		670
Ala Leu Asn Ile Ser Asn Ser Val Arg Arg Gly Asn Phe Thr Glu Ala						
		675		680		685
Phe Ala Val Thr Gly Val Thr Ile Leu Leu Glu Ala Phe Pro Glu Phe						
		690		695		700
Thr Ile Pro Ala Leu Gly Ala Phe Val Ile Tyr Ser Lys Val Gln Glu						
		705		710		715
						720

Arg Asn Glu Ile Ile Lys Thr Ile Asp Asn Cys Leu Glu Gln Arg Ile
 725 730 735

Lys Arg Trp Lys Asp Ser Tyr Glu Trp Met Met Gly Thr Trp Leu Ser
 740 745 750

Arg Ile Ile Thr Gln Phe Asn Asn Ile Ser Tyr Gln Met Tyr Asp Ser
 755 760 765

Leu Asn Tyr Gln Ala Gly Ala Ile Lys Ala Lys Ile Asp Leu Glu Tyr
 770 775 780

Lys Lys Tyr Ser Gly Ser Asp Lys Glu Asn Ile Lys Ser Gln Val Glu
 785 790 795 800

Asn Leu Lys Asn Ser Leu Asp Val Lys Ile Ser Glu Ala Met Asn Asn
 805 810 815

Ile Asn Lys Phe Ile Arg Glu Cys Ser Val Thr Tyr Leu Phe Lys Asn
 820 825 830

Met Leu Pro Lys Val Ile Asp Glu Leu Asn Glu Phe Asp Arg Asn Thr
 835 840 845

Lys Ala Lys Leu Ile Asn Leu Ile Asp Ser His Asn Ile Ile Leu Val
 850 855 860

Gly Glu Val Asp Lys Leu Lys Ala Lys Val Asn Asn Ser Phe Gln Asn
 865 870 875 880

Thr Ile Pro Phe Asn Ile Phe Ser Tyr Thr Asn Asn Ser Leu Leu Lys
 885 890 895

Asp Ile Ile Asn Glu Tyr Phe Asn
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<210> 27
 <211> 1302
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 27
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ctgaacccgc caccggaagc gaaacaggtg cgggtatctt actatgactc cacctacctg 240
tctaccgata acgaaaagga caactacctg aaagggtgta ctaaactgtt cgagcgtatt 300
tactccaccg acctgggccc tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360
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cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480
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<210> 28

<211> 1257

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 28

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<220>
 <223> Synthetic

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 ttcaacaaga gtagcgggat tttcaatcgt gacgtctgcy agtactatga tccagattat 240
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<212> DNA
<213> Artificial Sequence

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<220>
<223> Synthetic

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cagccgggcta tcaagaaaat cttcaccgac gaaaacacca tcttccagta cctgtacagc   300
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 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 31
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 tttcgtatca ccggcaacat ttgggttatt ccggatcgtt ttagccgtaa cagcaacccg 180
 aatctgaata aaccgcccgcg tgttaccagc ccgaaaagcg gttattacga tccgaactat 240
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 gatgttaaaa cccgccaggg taacaattgg gtgaaaaccg gcagcattaa cccgagcgtg 480
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<210> 32

<211> 1263

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 32

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 taccgggata acgtgagcgt tgatcagggtg atcctgagca aaaacaccag cgaacatggt 180
 cagctggatc tgctgtatcc gagcattgat agcgaaagcg aaattctgcc gggcgaaaac 240
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<210> 33
 <211> 207
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 33
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 ggcggtggcg gtagcggcgg tggcggtagc ggcggtggcg gtagcgcact agtgctgcag 180
 acgcacggtc tagaatgata aaagctt 207

<210> 34
 <211> 108
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 34
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<210> 35
 <211> 186
 <212> DNA
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<220>
 <223> Synthetic

<400> 35
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<223> Synthetic

<400> 36

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agcggcggtg gcggtagcgc actagtgtg cagacgcacg gtctagaatg ataaaagctt 180

<210> 37

<211> 249

<212> DNA

<213> Artificial Sequence

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<223> Synthetic

<400> 37

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gctatcatca aaaacgctta caaaaaaggt gaagcgctag cgggtgggtg tggttctggt 180

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<210> 38

<211> 207

<212> DNA

<213> Artificial Sequence

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<223> Synthetic

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<210> 39

<211> 2709

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 39

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<210> 40
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<212> PRT
<213> Artificial Sequence

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<220>
<223> Synthetic

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<400> 40

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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
          20             25             30

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Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
          35             40             45

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Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
          50             55             60

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Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65             70             75             80

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Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp

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		355					360					365					
Leu	Asn	Phe	Asp	Lys	Ala	Val	Phe	Lys	Ile	Asn	Ile	Val	Pro	Lys	Val		
	370					375					380						
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385					390					395					400		
Ala	Asn	Phe	Asn	Gly	Gln	Asn	Thr	Glu	Ile	Asn	Asn	Met	Asn	Phe	Thr		
				405					410					415			
Lys	Leu	Lys	Asn	Phe	Thr	Gly	Leu	Phe	Glu	Phe	Tyr	Lys	Leu	Leu	Cys		
			420					425					430				
Val	Asp	Gly	Ile	Ile	Thr	Ser	Lys	Thr	Lys	Ser	Leu	Ile	Glu	Gly	Arg		
		435					440					445					
Phe	Gly	Gly	Phe	Thr	Gly	Ala	Arg	Lys	Ser	Ala	Arg	Lys	Leu	Ala	Asn		
	450					455					460						
Gln	Ala	Leu	Ala	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly		
465					470					475					480		
Gly	Gly	Ser	Ala	Leu	Val	Leu	Gln	Cys	Ile	Lys	Val	Asn	Asn	Trp	Asp		
				485					490					495			
Leu	Phe	Phe	Ser	Pro	Ser	Glu	Asp	Asn	Phe	Thr	Asn	Asp	Leu	Asn	Lys		
			500					505					510				
Gly	Glu	Glu	Ile	Thr	Ser	Asp	Thr	Asn	Ile	Glu	Ala	Ala	Glu	Glu	Asn		
			515				520					525					
Ile	Ser	Leu	Asp	Leu	Ile	Gln	Gln	Tyr	Tyr	Leu	Thr	Phe	Asn	Phe	Asp		
	530					535					540						
Asn	Glu	Pro	Glu	Asn	Ile	Ser	Ile	Glu	Asn	Leu	Ser	Ser	Asp	Ile	Ile		
545					550					555				560			
Gly	Gln	Leu	Glu	Leu	Met	Pro	Asn	Ile	Glu	Arg	Phe	Pro	Asn	Gly	Lys		
				565					570					575			

Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln
580 585 590

Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn
595 600 605

Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp
610 615 620

Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly
625 630 635 640

Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val
645 650 655

Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile
660 665 670

Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val
675 680 685

Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro
690 695 700

Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile
705 710 715 720

Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys
725 730 735

Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp
740 745 750

Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys
755 760 765

Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr
770 775 780

Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn
785 790 795 800

Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met
805 810 815

Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
820 825 830

Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
835 840 845

Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
850 855 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
865 870 875 880

Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg
885 890 895

Leu Leu Ser Thr Leu Asp
900

<210> 41
<211> 2736
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 41
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cctaggggat ccatggagtt cgtaacaaa cagttcaact ataaagaccc agttaacggt 180
gttgacattg cttacatcaa aatcccgaac gctggccaga tgcagccggt aaaggcattc 240
aaaatccaca aaaaaatctg gggtatcccg gaacgtgata cctttactaa cccggaagaa 300
ggtgacctga acccgccacc ggaagcgaaa cagggtgccg tatcttacta tgactccacc 360
tacctgtcta ccgataacga aaaggacaac tacctgaaag gtgttactaa actgttcgag 420
cgtatttact ccaccgacct gggccgtatg ctgctgacta gcatcgttcg cggatatccc 480
ttctggggcg gttctacat cgataccgaa ctgaaagtaa tcgacactaa ctgcatcaac 540
gttattcagc cggacggttc ctatcgttcc gaagaactga acctgggtgat catcggcccc 600
tctgctgata tcatccagtt cgagtgtgaa agctttggtc acgaagttct gaacctcacc 660
cgtaacggct acggttccac tcagtacatc cgtttctctc cggacttcac cttcggtttt 720
gaagaatccc tggaagtaga cacgaacca ctgctgggag ctggtaaatt cgcaactgat 780
cctgcgggta ccctgggtca cgaactgatt catgcaggcc accgcctgta cggtatcgcc 840

atcaatccga accgtgtctt caaagttaac accaacgcgt attacgagat gtccggtctg	900
gaagttagct tcgaagaact gcgtactttt ggcggtcacg acgctaaatt catcgactct	960
ctgcaagaaa acgagttccg tctgtactac tataacaagt tcaaagatat cgcattccacc	1020
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tttaaagaaa aatacctgct cagcgaagac acctccggca aattctctgt agacaagttg	1140
aaattcgata aactttacaa aatgctgact gaaatttaca ccgaagacaa cttcggttaag	1200
ttcttttaaag ttctgaaccg caaacctat ctgaacttcg acaaggcagt attcaaaatc	1260
aacatcgtgc cgaaagttaa ctacactatc tacgatgggt tcaacctgcg taacaccaac	1320
ctggctgcta attttaacgg ccagaacacg gaaatcaaca acatgaactt cacaaaaactg	1380
aaaaacttca ctgggtctggt cgagttttac aagctgctgt gcgtcgacgg catcattacc	1440
tccaaaacta aatctctgat agaaggtaga aacaaagcgc tgaacgacct ctgtatcaag	1500
gttaacaact gggatttatt cttcagcccg agtgaagaca acttcaccaa cgacctgaac	1560
aaagggtgaag aaatcacctc agatactaac atcgaagcag ccgaagaaaa catctcgctg	1620
gacctgatcc agcagtacta cctgaccttt aatttcgaca acgagccgga aaacatttct	1680
atcgaaaacc tgagctctga tatcatcggc cagctggaac tgatgccgaa catcgaacgt	1740
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ctcaaccctg cccgtgtata caccttcttc tctagcgact acgtgaaaaa ggtcaacaaa	1920
gcgactgaag ctgcaatggt cttgggttgg gttgaacagc ttgtttatga ttttaccgac	1980
gagacgtccg aagtatctac taccgacaaa attgcggata tcaactatcat catcccgtac	2040
atcgggtccg ctctgaacat tggcaacatg ctgtacaaag acgacttcgt tggcgactg	2100
atcttctccg gtgcggtgat cctgctggag ttcaccccg aaatcgccat cccggtactg	2160
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aacgcgctga gcaaacgtaa cgaaaaatgg gatgaagttt acaaatatat cgtgaccaac	2280
tggctggcta aggttaatac tcagatcgac ctcatccgca aaaaaatgaa agaagcactg	2340
gaaaaccagg cggaagctac caaggcaatc attactacc agtacaacca gtacaccgag	2400
gaagaaaaaa acaacatcaa cttcaacatc gacgatctgt cctctaaact gaacgaatcc	2460
atcaacaaag ctatgatcaa catcaacaag ttctgaacc agtgctctgt aagctatctg	2520
atgaactcca tgatcccgta cgggtgtaaa cgtctggagg acttcgatgc gtctctgaaa	2580
gacgcctgc tgaaatacat ttacgacaac cgtggcactc tgatcggtca ggttgatcgt	2640

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 gtcgataacc aacgcctttt gtccactcta gactag 2736

<210> 42
 <211> 911
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 42

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Ala Arg Lys Leu Ala Asn Gln Thr Ser Gly Gly Gly Gly Ser Gly Gly
 20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Pro Arg Gly Ser Met Glu Phe Val
 35 40 45

Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly Val Asp Ile Ala
 50 55 60

Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro Val Lys Ala Phe
 65 70 75 80

Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg Asp Thr Phe Thr
 85 90 95

Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro Pro Glu Ala Lys Gln Val
 100 105 110

Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr Asp Asn Glu Lys
 115 120 125

Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu Arg Ile Tyr Ser
 130 135 140

Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val Arg Gly Ile Pro
 145 150 155 160

Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys Val Ile Asp Thr
 165 170 175

Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr Arg Ser Glu Glu
 180 185 190

Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile Ile Gln Phe Glu
 195 200 205

Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr Arg Asn Gly Tyr
 210 215 220

Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe Thr Phe Gly Phe
 225 230 235 240

Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu Gly Ala Gly Lys
 245 250 255

Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu Leu Ile His Ala
 260 265 270

Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn Arg Val Phe Lys
 275 280 285

Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu Glu Val Ser Phe
 290 295 300

Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys Phe Ile Asp Ser
 305 310 315 320

Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn Lys Phe Lys Asp
 325 330 335

Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser Ile Val Gly Thr Thr Ala
 340 345 350

Ser Leu Gln Tyr Met Lys Asn Val Phe Lys Glu Lys Tyr Leu Leu Ser
 355 360 365

Glu Asp Thr Ser Gly Lys Phe Ser Val Asp Lys Leu Lys Phe Asp Lys
 370 375 380

Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr Glu Asp Asn Phe Val Lys
 385 390 395 400

Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr Leu Asn Phe Asp Lys Ala
 405 410 415

Val Phe Lys Ile Asn Ile Val Pro Lys Val Asn Tyr Thr Ile Tyr Asp
 420 425 430

Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala Ala Asn Phe Asn Gly Gln
 435 440 445

Asn Thr Glu Ile Asn Asn Met Asn Phe Thr Lys Leu Lys Asn Phe Thr
 450 455 460

Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys Val Asp Gly Ile Ile Thr
 465 470 475 480

Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg Asn Lys Ala Leu Asn Asp
 485 490 495

Leu Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu
 500 505 510

Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp
 515 520 525

Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln
 530 535 540

Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser
 545 550 555 560

Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro
 565 570 575

Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr
 580 585 590

Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser
 595 600 605

Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser
 610 615 620

Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys
 625 630 635 640

Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr
 645 650 655

Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala
 660 665 670

Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly
675 680 685

Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly
690 695 700

Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu
705 710 715 720

Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val
725 730 735

Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu
740 745 750

Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln
755 760 765

Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala
770 775 780

Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu
785 790 795 800

Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys
805 810 815

Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu
820 825 830

Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly
835 840 845

Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu
850 855 860

Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg
865 870 875 880

Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln
885 890 895

Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
900 905 910

<211> 2715
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 43
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tttcgtatca cgggcaacat ttgggttatt ccggatcggt ttagccgtaa cagcaaccgcg 180
aatctgaata aaccgccgcg tgttaccagc ccgaaaagcg gttattacga tccgaactat 240
ctgagcaccg atagcgataa agataccttc ctgaaagaaa tcatcaaact gttcaaacgc 300
atcaacagcc gtgaaattgg cgaagaactg atctatcgcc tgagcaccga tattccggtt 360
ccgggcaaca acaacacccc gatcaacacc ttgatttcg atgtggattt caacagcggt 420
gatgttaaaa cccgccaggg taacaattgg gtgaaaaccg gcagcattaa cccgagcgtg 480
attattaccg gtccgcgcga aaacattatt gatccggaaa ccagcacctt taaactgacc 540
aacaacacct ttgcggcgca ggaagggtttt ggcgcgctga gcattattag cattagcccg 600
cgctttatgc tgacctatag caacgcgacc aacgatgttg gtgaaggccg tttcagcaaa 660
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aacctgtatg gcatcgcgat tccgaacgat cagaccatta gcagcgtgac cagcaacatc 780
ttttacagcc agtacaacgt gaaactggaa tatgcggaaa tctatgcgtt tggcgggtccg 840
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tttattggcg atatcagcga tgtgaaaacc gatattctcc tgcgcaaaga tatcaacgaa 1560
gaaaccgaag tgatctacta cccggataac gtgagcggtg atcaggtgat cctgagcaaa 1620

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aacaccagcg aacatggtca gctggatctg ctgtatccga gcattgatag cgaaagcgaa 1680
attctgccgg gcgaaaacca ggtgttttac gataaccgta cccagaacgt ggattacctg 1740
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ggcaatttta ccgaagcgtt tgcggttacc ggtgtgacca ttctgctgga agcgtttccg 2100
gaattttacca ttccggcgct ggggtgcgttt gtgatctata gcaaagtgc ggaacgcaac 2160
gaaatcatca aaaccatcga taactgcctg gaacagcgta ttaaagctg gaaagatagc 2220
tatgaatgga tgatgggcac ctggctgagc cgtattatca cccagttcaa caacatcagc 2280
taccagatgt acgatagcct gaactatcag gcgggtgcga ttaaagcgaa aatcgatctg 2340
gaatacaaaa aatacagcgg cagcgataaa gaaaacatca aaagccaggt tgaaaacctg 2400
aaaaacagcc tggatgtgaa aattagcgaa gcgatgaata acatcaacaa attcatccgc 2460
gaatgcagcg tgacctacct gttcaaaaac atgctgccga aagtgatcga tgaactgaac 2520
gaatttgatc gcaacaccaa agcgaaactg atcaacctga tcgatagcca caacattatt 2580
ctggtgggcg aagtggataa actgaaagcg aaagttaaca acagcttcca gaacaccatc 2640
ccgtttaaca tcttcagcta taccaacaac agcctgctga aagatatcat caacgaatac 2700
ttcaatctag actag 2715

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<210> 44

<211> 904

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 44

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Gly Ser Glu Phe Met Pro Ile Thr Ile Asn Asn Phe Asn Tyr Ser Asp
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Pro Val Asp Asn Lys Asn Ile Leu Tyr Leu Asp Thr His Leu Asn Thr
          20           25           30

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Leu Ala Asn Glu Pro Glu Lys Ala Phe Arg Ile Thr Gly Asn Ile Trp
          35           40           45

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Val Ile Pro Asp Arg Phe Ser Arg Asn Ser Asn Pro Asn Leu Asn Lys
 50 55 60

Pro Pro Arg Val Thr Ser Pro Lys Ser Gly Tyr Tyr Asp Pro Asn Tyr
 65 70 75 80

Leu Ser Thr Asp Ser Asp Lys Asp Thr Phe Leu Lys Glu Ile Ile Lys
 85 90 95

Leu Phe Lys Arg Ile Asn Ser Arg Glu Ile Gly Glu Glu Leu Ile Tyr
 100 105 110

Arg Leu Ser Thr Asp Ile Pro Phe Pro Gly Asn Asn Asn Thr Pro Ile
 115 120 125

Asn Thr Phe Asp Phe Asp Val Asp Phe Asn Ser Val Asp Val Lys Thr
 130 135 140

Arg Gln Gly Asn Asn Trp Val Lys Thr Gly Ser Ile Asn Pro Ser Val
 145 150 155 160

Ile Ile Thr Gly Pro Arg Glu Asn Ile Ile Asp Pro Glu Thr Ser Thr
 165 170 175

Phe Lys Leu Thr Asn Asn Thr Phe Ala Ala Gln Glu Gly Phe Gly Ala
 180 185 190

Leu Ser Ile Ile Ser Ile Ser Pro Arg Phe Met Leu Thr Tyr Ser Asn
 195 200 205

Ala Thr Asn Asp Val Gly Glu Gly Arg Phe Ser Lys Ser Glu Phe Cys
 210 215 220

Met Asp Pro Ile Leu Ile Leu Met His Glu Leu Asn His Ala Met His
 225 230 235 240

Asn Leu Tyr Gly Ile Ala Ile Pro Asn Asp Gln Thr Ile Ser Ser Val
 245 250 255

Thr Ser Asn Ile Phe Tyr Ser Gln Tyr Asn Val Lys Leu Glu Tyr Ala
 260 265 270

Glu Ile Tyr Ala Phe Gly Gly Pro Thr Ile Asp Leu Ile Pro Lys Ser
 275 280 285

Ala Arg Lys Tyr Phe Glu Glu Lys Ala Leu Asp Tyr Tyr Arg Ser Ile
 290 295 300

Ala Lys Arg Leu Asn Ser Ile Thr Thr Ala Asn Pro Ser Ser Phe Asn
 305 310 315 320

Lys Tyr Ile Gly Glu Tyr Lys Gln Lys Leu Ile Arg Lys Tyr Arg Phe
 325 330 335

Val Val Glu Ser Ser Gly Glu Val Thr Val Asn Arg Asn Lys Phe Val
 340 345 350

Glu Leu Tyr Asn Glu Leu Thr Gln Ile Phe Thr Glu Phe Asn Tyr Ala
 355 360 365

Lys Ile Tyr Asn Val Gln Asn Arg Lys Ile Tyr Leu Ser Asn Val Tyr
 370 375 380

Thr Pro Val Thr Ala Asn Ile Leu Asp Asp Asn Val Tyr Asp Ile Gln
 385 390 395 400

Asn Gly Phe Asn Ile Pro Lys Ser Asn Leu Asn Val Leu Phe Met Gly
 405 410 415

Gln Asn Leu Ser Arg Asn Pro Ala Leu Arg Lys Val Asn Pro Glu Asn
 420 425 430

Met Leu Tyr Leu Phe Thr Lys Phe Cys Val Asp Ala Ile Asp Gly Arg
 435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Leu Ala Asn
 450 455 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
 465 470 475 480

Gly Gly Ser Ala Leu Val Leu Gln Cys Arg Glu Leu Leu Val Lys Asn
 485 490 495

Thr Asp Leu Pro Phe Ile Gly Asp Ile Ser Asp Val Lys Thr Asp Ile
 500 505 510

Phe Leu Arg Lys Asp Ile Asn Glu Glu Thr Glu Val Ile Tyr Tyr Pro
 515 520 525

Asp Asn Val Ser Val Asp Gln Val Ile Leu Ser Lys Asn Thr Ser Glu

530		535		540
His Gly Gln Leu Asp	Leu Leu Tyr Pro Ser	Ile Asp Ser Glu Ser Glu		
545	550	555		560
Ile Leu Pro Gly Glu Asn Gln Val Phe Tyr Asp Asn Arg Thr Gln Asn				
	565	570		575
Val Asp Tyr Leu Asn Ser Tyr Tyr Tyr Leu Glu Ser Gln Lys Leu Ser				
	580	585		590
Asp Asn Val Glu Asp Phe Thr Phe Thr Arg Ser Ile Glu Glu Ala Leu				
	595	600		605
Asp Asn Ser Ala Lys Val Tyr Thr Tyr Phe Pro Thr Leu Ala Asn Lys				
	610	615		620
Val Asn Ala Gly Val Gln Gly Gly Leu Phe Leu Met Trp Ala Asn Asp				
	625	630		640
Val Val Glu Asp Phe Thr Thr Asn Ile Leu Arg Lys Asp Thr Leu Asp				
	645	650		655
Lys Ile Ser Asp Val Ser Ala Ile Ile Pro Tyr Ile Gly Pro Ala Leu				
	660	665		670
Asn Ile Ser Asn Ser Val Arg Arg Gly Asn Phe Thr Glu Ala Phe Ala				
	675	680		685
Val Thr Gly Val Thr Ile Leu Leu Glu Ala Phe Pro Glu Phe Thr Ile				
	690	695		700
Pro Ala Leu Gly Ala Phe Val Ile Tyr Ser Lys Val Gln Glu Arg Asn				
	705	710		715
Glu Ile Ile Lys Thr Ile Asp Asn Cys Leu Glu Gln Arg Ile Lys Arg				
	725	730		735
Trp Lys Asp Ser Tyr Glu Trp Met Met Gly Thr Trp Leu Ser Arg Ile				
	740	745		750
Ile Thr Gln Phe Asn Asn Ile Ser Tyr Gln Met Tyr Asp Ser Leu Asn				
	755	760		765
Tyr Gln Ala Gly Ala Ile Lys Ala Lys Ile Asp Leu Glu Tyr Lys Lys				
	770	775		780

Tyr Ser Gly Ser Asp Lys Glu Asn Ile Lys Ser Gln Val Glu Asn Leu
785 790 795 800

Lys Asn Ser Leu Asp Val Lys Ile Ser Glu Ala Met Asn Asn Ile Asn
805 810 815

Lys Phe Ile Arg Glu Cys Ser Val Thr Tyr Leu Phe Lys Asn Met Leu
820 825 830

Pro Lys Val Ile Asp Glu Leu Asn Glu Phe Asp Arg Asn Thr Lys Ala
835 840 845

Lys Leu Ile Asn Leu Ile Asp Ser His Asn Ile Ile Leu Val Gly Glu
850 855 860

Val Asp Lys Leu Lys Ala Lys Val Asn Asn Ser Phe Gln Asn Thr Ile
865 870 875 880

Pro Phe Asn Ile Phe Ser Tyr Thr Asn Asn Ser Leu Leu Lys Asp Ile
885 890 895

Ile Asn Glu Tyr Phe Asn Leu Asp
900

<210> 45
<211> 2742
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 45
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aatctgaata aaccgccgcg tgttaccagc ccgaaaagcg gttattacga tccgaactat 240
ctgagcaccg atagcgataa agataccttc ctgaaagaaa tcatcaaact gttcaaacgc 300
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ccgggcaaca acaacacccc gatcaacacc ttgatttcg atgtggattt caacagcggt 420
gatgttaaaa cccgccaggg taacaattgg gtgaaaaccg gcagcattaa cccgagcgtg 480
attattaccg gtccgcgcga aaacattatt gatecggaaa ccagcacctt taaactgacc 540

aacaacacct ttgcggcgca ggaaggtttt ggcgcgctga gcattattag cattagcccg	600
cgcttttatgc tgacctatag caacgcgacc aacgatgttg gtgaaggccg tttcagcaaaa	660
agcgaatttt gcatggaccc gatcctgatc ctgatgcatg aactgaacca tgcgatgcat	720
aacctgtatg gcatcgcgat tccgaacgat cagaccatta gcagcgtgac cagcaacatc	780
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atcttcaccg aatttaacta tgcgaaaatc tataacgtgc agaaccgtaa aatctacctg	1140
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<210> 46
 <211> 913
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 46

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Pro Val Asp Asn Lys Asn Ile Leu Tyr Leu Asp Thr His Leu Asn Thr
 20 25 30

Leu Ala Asn Glu Pro Glu Lys Ala Phe Arg Ile Thr Gly Asn Ile Trp
 35 40 45

Val Ile Pro Asp Arg Phe Ser Arg Asn Ser Asn Pro Asn Leu Asn Lys
 50 55 60

Pro Pro Arg Val Thr Ser Pro Lys Ser Gly Tyr Tyr Asp Pro Asn Tyr
 65 70 75 80

Leu Ser Thr Asp Ser Asp Lys Asp Thr Phe Leu Lys Glu Ile Ile Lys
 85 90 95

Leu Phe Lys Arg Ile Asn Ser Arg Glu Ile Gly Glu Glu Leu Ile Tyr
 100 105 110

Arg Leu Ser Thr Asp Ile Pro Phe Pro Gly Asn Asn Asn Thr Pro Ile
 115 120 125

Asn Thr Phe Asp Phe Asp Val Asp Phe Asn Ser Val Asp Val Lys Thr
 130 135 140

Arg Gln Gly Asn Asn Trp Val Lys Thr Gly Ser Ile Asn Pro Ser Val

145		150		155		160
Ile Ile Thr Gly	Pro Arg Glu Asn Ile	Ile Asp Pro Glu Thr	Ser Thr			
	165		170		175	
Phe Lys Leu Thr	Asn Asn Thr Phe	Ala Ala Gln Glu Gly	Phe Gly Ala			
	180	185	190			
Leu Ser Ile Ile	Ser Ile Ser Pro Arg Phe	Met Leu Thr Tyr	Ser Asn			
	195	200	205			
Ala Thr Asn Asp	Val Gly Glu Gly Arg Phe	Ser Lys Ser Glu Phe	Cys			
	210	215	220			
Met Asp Pro Ile	Leu Ile Leu Met His Glu	Leu Asn His Ala Met	His			
	225	230	235		240	
Asn Leu Tyr Gly	Ile Ala Ile Pro Asn Asp	Gln Thr Ile Ser	Ser Val			
	245	250	255			
Thr Ser Asn Ile	Phe Tyr Ser Gln Tyr Asn	Val Lys Leu Glu Tyr	Ala			
	260	265	270			
Glu Ile Tyr Ala	Phe Gly Gly Pro Thr Ile	Asp Leu Ile Pro Lys	Ser			
	275	280	285			
Ala Arg Lys Tyr	Phe Glu Glu Lys Ala Leu	Asp Tyr Tyr Arg Ser	Ile			
	290	295	300			
Ala Lys Arg Leu	Asn Ser Ile Thr Thr Ala	Asn Pro Ser Ser Phe	Asn			
	305	310	315		320	
Lys Tyr Ile Gly	Glu Tyr Lys Gln Lys Leu	Ile Arg Lys Tyr Arg	Phe			
	325	330	335			
Val Val Glu Ser	Ser Gly Glu Val Thr Val	Asn Arg Asn Lys Phe	Val			
	340	345	350			
Glu Leu Tyr Asn	Glu Leu Thr Gln Ile Phe Thr	Glu Phe Asn Tyr Ala				
	355	360	365			
Lys Ile Tyr Asn	Val Gln Asn Arg Lys Ile Tyr	Leu Ser Asn Val Tyr				
	370	375	380			
Thr Pro Val Thr	Ala Asn Ile Leu Asp Asp	Asn Val Tyr Asp Ile	Gln			
	385	390	395		400	

Asn Gly Phe Asn Ile Pro Lys Ser Asn Leu Asn Val Leu Phe Met Gly
 405 410 415

Gln Asn Leu Ser Arg Asn Pro Ala Leu Arg Lys Val Asn Pro Glu Asn
 420 425 430

Met Leu Tyr Leu Phe Thr Lys Phe Cys Val Asp Gly Ile Ile Thr Ser
 435 440 445

Lys Thr Lys Ser Leu Ile Glu Gly Arg Phe Gly Gly Phe Thr Gly Ala
 450 455 460

Arg Lys Ser Ala Arg Lys Leu Ala Asn Gln Ala Leu Ala Gly Gly Gly
 465 470 475 480

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Ala Leu Val Leu
 485 490 495

Gln Cys Arg Glu Leu Leu Val Lys Asn Thr Asp Leu Pro Phe Ile Gly
 500 505 510

Asp Ile Ser Asp Val Lys Thr Asp Ile Phe Leu Arg Lys Asp Ile Asn
 515 520 525

Glu Glu Thr Glu Val Ile Tyr Tyr Pro Asp Asn Val Ser Val Asp Gln
 530 535 540

Val Ile Leu Ser Lys Asn Thr Ser Glu His Gly Gln Leu Asp Leu Leu
 545 550 555 560

Tyr Pro Ser Ile Asp Ser Glu Ser Glu Ile Leu Pro Gly Glu Asn Gln
 565 570 575

Val Phe Tyr Asp Asn Arg Thr Gln Asn Val Asp Tyr Leu Asn Ser Tyr
 580 585 590

Tyr Tyr Leu Glu Ser Gln Lys Leu Ser Asp Asn Val Glu Asp Phe Thr
 595 600 605

Phe Thr Arg Ser Ile Glu Glu Ala Leu Asp Asn Ser Ala Lys Val Tyr
 610 615 620

Thr Tyr Phe Pro Thr Leu Ala Asn Lys Val Asn Ala Gly Val Gln Gly
 625 630 635 640

Gly Leu Phe Leu Met Trp Ala Asn Asp Val Val Glu Asp Phe Thr Thr
 645 650 655

Asn Ile Leu Arg Lys Asp Thr Leu Asp Lys Ile Ser Asp Val Ser Ala
 660 665 670

Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Ser Asn Ser Val Arg
 675 680 685

Arg Gly Asn Phe Thr Glu Ala Phe Ala Val Thr Gly Val Thr Ile Leu
 690 695 700

Leu Glu Ala Phe Pro Glu Phe Thr Ile Pro Ala Leu Gly Ala Phe Val
 705 710 715 720

Ile Tyr Ser Lys Val Gln Glu Arg Asn Glu Ile Ile Lys Thr Ile Asp
 725 730 735

Asn Cys Leu Glu Gln Arg Ile Lys Arg Trp Lys Asp Ser Tyr Glu Trp
 740 745 750

Met Met Gly Thr Trp Leu Ser Arg Ile Ile Thr Gln Phe Asn Asn Ile
 755 760 765

Ser Tyr Gln Met Tyr Asp Ser Leu Asn Tyr Gln Ala Gly Ala Ile Lys
 770 775 780

Ala Lys Ile Asp Leu Glu Tyr Lys Lys Tyr Ser Gly Ser Asp Lys Glu
 785 790 795 800

Asn Ile Lys Ser Gln Val Glu Asn Leu Lys Asn Ser Leu Asp Val Lys
 805 810 815

Ile Ser Glu Ala Met Asn Asn Ile Asn Lys Phe Ile Arg Glu Cys Ser
 820 825 830

Val Thr Tyr Leu Phe Lys Asn Met Leu Pro Lys Val Ile Asp Glu Leu
 835 840 845

Asn Glu Phe Asp Arg Asn Thr Lys Ala Lys Leu Ile Asn Leu Ile Asp
 850 855 860

Ser His Asn Ile Ile Leu Val Gly Glu Val Asp Lys Leu Lys Ala Lys
 865 870 875 880

Val Asn Asn Ser Phe Gln Asn Thr Ile Pro Phe Asn Ile Phe Ser Tyr
 885 890 895

Thr Asn Asn Ser Leu Leu Lys Asp Ile Ile Asn Glu Tyr Phe Asn Leu
 900 905 910

Asp

<210> 47
 <211> 2673
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 47
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 cacaacaaaa tctgggttat ccggaacgt gataccttta ctaaccgga agaaggtgac 180
 ctgaaccgcg caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240
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 tactccaccg acctgggccc tatgtctgtg actagcatcg ttcgcggtat cccgttctgg 360
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 cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480
 gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct caccgtaac 540
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 ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780
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gataaccaac gccttttctc cactctagac tag 2673

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<210> 48
<211> 890
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 48

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
 20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
 35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
 50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
 65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
 85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
 100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
 115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
 130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
 145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
 165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
 180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
 210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser

245	250	255
Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp 260 265 270		
Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr 275 280 285		
Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser 290 295 300		
Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys 305 310 315 320		
Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp 325 330 335		
Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr 340 345 350		
Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr 355 360 365		
Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val 370 375 380		
Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala 385 390 395 400		
Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr 405 410 415		
Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys 420 425 430		
Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg 435 440 445		
Tyr Gly Gly Phe Met Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly 450 455 460		
Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val 465 470 475 480		
Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn 485 490 495		

Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala
 500 505 510

Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr
 515 520 525

Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser
 530 535 540

Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe
 545 550 555 560

Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr
 565 570 575

Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr
 580 585 590

Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe
 595 600 605

Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala
 610 615 620

Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu
 625 630 635 640

Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile
 645 650 655

Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys
 660 665 670

Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu
 675 680 685

Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu
 690 695 700

Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn
 705 710 715 720

Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile
 725 730 735

Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg
740 745 750

Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala
755 760 765

Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn
770 775 780

Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile
785 790 795 800

Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val
805 810 815

Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu
820 825 830

Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp
835 840 845

Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val
850 855 860

Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val
865 870 875 880

Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
885 890

<210> 49

<211> 2751

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 49

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ctgaaccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

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gaaaaatacc	tgctcagcga	agacacctcc	ggcaaattct	ctgtagacaa	gttgaaattc	1020
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gttaacgaag	ctctgctcaa	cccgtcccgt	gtatacacct	tcttctctag	cgactacgtg	1920
aaaaagggtca	acaaagcgac	tgaagctgca	atgttcttgg	gttgggttga	acagcttggt	1980
tatgatttta	ccgacgagac	gtccgaagta	tctactaccg	acaaaattgc	ggatatcact	2040
atcatcatcc	cgtacatcgg	tccggctctg	aacattggca	acatgctgta	caaagacgac	2100
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<210> 50
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 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 50

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Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
          20           25           30

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Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
          35           40           45

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Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
          50           55           60

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Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65           70           75           80

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Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
          85           90           95

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Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
          100          105          110

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Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
          115          120          125

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Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
 130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
 145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
 165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
 180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
 210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
 245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
 275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
 290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
 305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
 435 440 445

Tyr Gly Gly Phe Met Thr Ser Glu Lys Ser Gln Thr Pro Leu Val Thr
 450 455 460

Leu Phe Lys Asn Ala Ile Ile Lys Asn Ala Tyr Lys Lys Gly Glu Ala
 465 470 475 480

Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 485 490 495

Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe
 500 505 510

Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu
 515 520 525

Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser
 530 535 540

Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu
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Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln
 565 570 575

Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr
 580 585 590

Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe
 595 600 605

Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala
 610 615 620

Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val
 625 630 635 640

Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val
 645 650 655

Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr
 660 665 670

Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro
 675 680 685

Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala
 690 695 700

Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile
 705 710 715 720

Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn
 725 730 735

Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn
 740 745 750

Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala
 755 760 765

Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala
 770 775 780

Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr
 785 790 795 800

Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp
 805 810 815

Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn
 820 825 830

Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser
 835 840 845

Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu

850

855

860

Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile
 865 870 875 880

Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr
 885 890 895

Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu
 900 905 910

Ser Thr Leu Asp
 915

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 <211> 2709
 <212> DNA
 <213> Artificial Sequence

<220>
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 cacaacaaaa tctgggttat cccggaacgt gataccttta ctaaccgga agaaggtgac 180
 ctgaaccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240
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<211> 902
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 52

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 20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
 35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
 50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
 65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
 85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
 100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
 115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
 130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
 145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
 165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
 180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
 210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
 245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
 275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
 290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
 305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
 435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys Asn

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Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly				
465		470		475 480
Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp				
	485		490	495
Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys				
	500		505	510
Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn				
	515		520	525
Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp				
	530		535	540
Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile				
	545		550	555 560
Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys				
	565		570	575
Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln				
	580		585	590
Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn				
	595		600	605
Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp				
	610		615	620
Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly				
	625		630	635 640
Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val				
	645		650	655
Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile				
	660		665	670
Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val				
	675		680	685
Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro				
	690		695	700

Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile
705 710 715 720

Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys
725 730 735

Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp
740 745 750

Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys
755 760 765

Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr
770 775 780

Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn
785 790 795 800

Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met
805 810 815

Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
820 825 830

Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
835 840 845

Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
850 855 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
865 870 875 880

Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg
885 890 895

Leu Leu Ser Thr Leu Asp
900

<210> 53

<211> 2691

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<210> 54
 <211> 896
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 54

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
 20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
 35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
 50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
 65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
 85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
 100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
 115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
 130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
 145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
 165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
 180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
 210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
 245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
 275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
 290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
 305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
 435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Ala Leu Ala Gly Gly
 450 455 460

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Ala Leu Val
 465 470 475 480

Leu Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser
 485 490 495

Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser
 500 505 510

Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile
 515 520 525

Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile
 530 535 540

Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met
 545 550 555 560

Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys

565	570	575
Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys		
580	585	590
Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro		
595	600	605
Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn		
610	615	620
Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val		
625	630	635
Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile		
645	650	655
Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile		
660	665	670
Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser		
675	680	685
Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val		
690	695	700
Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr		
705	710	715
Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp		
725	730	735
Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr		
740	745	750
Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln		
755	760	765
Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr		
770	775	780
Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser		
785	790	795
Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe		
805	810	815

Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr
 820 825 830

Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu
 835 840 845

Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp
 850 855 860

Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe
 865 870 875 880

Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
 885 890 895

<210> 55
 <211> 2691
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 55
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 cacaacaaaa tctgggttat cccggaacgt gataccttta ctaaccgga agaaggtgac 180
 ctgaaccgc caccggaagc gaaacaggtg cgggtatctt actatgactc cacctacctg 240
 tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300
 tactccaccg acctgggccc tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360
 ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420
 cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480
 gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct caccgtaac 540
 ggctacggtt ccaactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600
 tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660
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 ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780
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aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa	960
gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc	1020
gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt	1080
aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc	1140
gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct	1200
gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac	1260
ttcactggtc tgttcgagtt ttacaagctg ctgtgcgtcg acggcatcat tacctccaaa	1320
actaaatctc tgatagaagg tagatttggc ggtttcacgg gcgcacgcaa atatgcggcg	1380
ctagcgggcg gtggcggtag cggcggtggc ggtagcggcg gtggcggtag cgactagtg	1440
ctgcagtgta tcaaggttaa caactgggat ttattcttca gcccagtgta agacaacttc	1500
accaacgacc tgaacaaagg tgaagaaatc acctcagata ctaacatcga agcagccgaa	1560
gaaaacatct cgctggacct gatccagcag tactacctga cctttaattt cgacaacgag	1620
ccggaaaaca tttctatcga aaacctgagc tctgatatca tcggccagct ggaactgatg	1680
ccgaacatcg aacgtttccc aaacggtaaa aagtacgagc tggacaaata taccatgttc	1740
cactacctgc gcgcgcagga atttgaacac ggcaaatccc gtatcgact gactaactcc	1800
gttaacgaag ctctgctcaa cccgtcccgt gtatacacct tcttctctag cgactacgtg	1860
aaaaagggtca acaaagcgac tgaagctgca atgttcttgg gttgggttga acagcttggt	1920
tatgatttta ccgacgagac gtccgaagta tctactaccg acaaaattgc ggatatcact	1980
atcatcatcc cgtacatcgg tccggctctg aacattggca acatgctgta caaagacgac	2040
ttcgttggcg cactgatctt ctccggtgcg gtgatcctgc tggagttcat cccggaaatc	2100
gccatcccgg tactgggcac ctttgctctg gtttcttaca ttgcaaacaa ggttctgact	2160
gtacaaacca tcgacaacgc gctgagcaaa cgtaacgaaa aatgggatga agtttacaaa	2220
tatatcgtga ccaactggct ggctaagggt aatactcaga tcgacctcat ccgcaaaaaa	2280
atgaaagaag cactggaaaa ccaggcgga gctaccaagg caatcattaa ctaccagtac	2340
aaccagtaca ccgaggaaga aaaaaacaac atcaacttca acatcgacga tctgtcctct	2400
aaactgaacg aatccatcaa caaagctatg atcaacatca acaagttcct gaaccagtgc	2460
tctgtaagct atctgatgaa ctccatgatc ccgtacggtg ttaaactgtt ggaggacttc	2520
gatgcgtctc tgaaagacgc cctgctgaaa tacatttacg acaaccgtgg cactctgatc	2580
ggtcagggtt atcgtctgaa ggacaaagtg aacaatacct tatcgaccga catccctttt	2640
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<210> 56
 <211> 896
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 56

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
 20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
 35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
 50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
 65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
 85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
 100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
 115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
 130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
 145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
 165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
 180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
 210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
 245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
 275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
 290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
 305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
 435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Tyr Ala Ala Leu Ala Gly Gly
 450 455 460

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Val
 465 470 475 480

Leu Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser
 485 490 495

Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser
 500 505 510

Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile
 515 520 525

Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile
 530 535 540

Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met
 545 550 555 560

Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys
 565 570 575

Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys
 580 585 590

Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro
 595 600 605

Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn
 610 615 620

Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val
 625 630 635 640

Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile
 645 650 655

Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile
 660 665 670

Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser
 675 680 685

Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val

690	695	700
Leu Gly Thr Phe Ala	Leu Val Ser Tyr Ile	Ala Asn Lys Val Leu Thr
705	710	715 720
Val Gln Thr Ile Asp	Asn Ala Leu Ser Lys Arg	Asn Glu Lys Trp Asp
725	730	735
Glu Val Tyr Lys Tyr Ile	Val Thr Asn Trp Leu	Ala Lys Val Asn Thr
740	745	750
Gln Ile Asp Leu Ile Arg	Lys Lys Met Lys Glu	Ala Leu Glu Asn Gln
755	760	765
Ala Glu Ala Thr Lys	Ala Ile Ile Asn Tyr	Gln Tyr Asn Gln Tyr Thr
770	775	780
Glu Glu Glu Lys Asn	Asn Ile Asn Phe Asn	Ile Asp Asp Leu Ser Ser
785	790	795 800
Lys Leu Asn Glu Ser	Ile Asn Lys Ala Met	Ile Asn Ile Asn Lys Phe
805	810	815
Leu Asn Gln Cys Ser	Val Ser Tyr Leu Met	Asn Ser Met Ile Pro Tyr
820	825	830
Gly Val Lys Arg Leu	Glu Asp Phe Asp	Ala Ser Leu Lys Asp Ala Leu
835	840	845
Leu Lys Tyr Ile Tyr	Asp Asn Arg Gly Thr	Leu Ile Gly Gln Val Asp
850	855	860
Arg Leu Lys Asp Lys	Val Asn Asn Thr Leu	Ser Thr Asp Ile Pro Phe
865	870	875 880
Gln Leu Ser Lys Tyr	Val Asp Asn Gln Arg	Leu Leu Ser Thr Leu Asp
885	890	895

<210> 57
 <211> 2691
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 57
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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaaccgga agaagggtgac	180
ctgaaccgcg caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg	240
tctaccgata acgaaaagga caactacctg aaagggtgta ctaaactgtt cgagcgtatt	300
tactccaccg acctgggccc tatgctgctg actagcatcg ttcgcggtat cccgttctgg	360
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cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct	480
gatatcatcc agttcgagtg taagagcttt ggctacgaag ttctgaacct caccgtaac	540
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tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg	660
gttaccctgg ctacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat	720
ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt	780
agcttcgaag aactgcgtac ttttggcggc cagcagcta aattcatcga ctctctgcaa	840
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gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt	1080
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ctagcgggcg gtggcggtag cggcggtggc ggtagcggcg gtggcggtag cgcactagtg	1440
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cactacctgc gcgcgagga atttgaacac ggcaaatccc gtatcgcaact gactaactcc	1800
gttaacgaag ctctgctcaa cccgtcccgt gtatacacct tcttctctag cgactacgtg	1860

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<210> 58
 <211> 896
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 58

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
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Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
 35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
 50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
 65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
 85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
 100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
 115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
 130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
 145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
 165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
 180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
 210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
 245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
 275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
 290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
 305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
 435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Tyr Ala Leu Ala Gly Gly
 450 455 460

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Val
 465 470 475 480

Leu Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser
 485 490 495

Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser
 500 505 510

Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile
 515 520 525

Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile
 530 535 540

Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met
 545 550 555 560

Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys
 565 570 575

Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys
 580 585 590

Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro
 595 600 605

Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn
 610 615 620

Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val
 625 630 635 640

Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile
 645 650 655

Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile
 660 665 670

Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser
 675 680 685

Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val
 690 695 700

Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr
 705 710 715 720

Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp
 725 730 735

Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr
 740 745 750

Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln
 755 760 765

Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr
 770 775 780

Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser
 785 790 795 800

Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe
 805 810 815

Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr

820	825	830
Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu		
835	840	845
Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp		
850	855	860
Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe		
865	870	875
Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp		
885	890	895

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 <211> 2709
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 59
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Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
 35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
 50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
 65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
 85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
 100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
 115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
 130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
 145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
 165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
 180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
 210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
 245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
 275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
 290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
 305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
 435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Tyr Ala Asn

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Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys				
	500		505	510
Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn				
	515		520	525
Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp				
	530		535	540
Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile				
	545		550	555
				560
Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys				
	565		570	575
Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln				
	580		585	590
Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn				
	595		600	605
Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp				
	610		615	620
Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly				
	625		630	635
				640
Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val				
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Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile				
	660		665	670
Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val				
	675		680	685
Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro				
	690		695	700

Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile
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Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys
725 730 735

Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp
740 745 750

Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys
755 760 765

Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr
770 775 780

Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn
785 790 795 800

Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met
805 810 815

Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
820 825 830

Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
835 840 845

Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
850 855 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
865 870 875 880

Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg
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Leu Leu Ser Thr Leu Asp
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<212> PRT

<213> Artificial Sequence

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<223> Synthetic

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          20           25           30

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Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
          35           40           45

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Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
          50           55           60

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Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65           70           75           80

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Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
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Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
 435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Ala Leu Ala
 450 455 460

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
 465 470 475 480

Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser
 485 490 495

Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile
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Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp
 515 520 525

Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu
 530 535 540

Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu
 545 550 555 560

Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu

110

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Trp	Asp	Glu	Val	Tyr	Lys	Tyr	Ile	Val	Thr	Asn	Trp	Leu	Ala	Lys	Val																																
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Tyr	Thr	Glu	Glu	Glu	Lys	Asn	Asn	Ile	Asn	Phe	Asn	Ile	Asp	Asp	Leu																																
			785			790						795																																			
Ser	Ser	Lys	Leu	Asn	Glu	Ser	Ile	Asn	Lys	Ala	Met	Ile	Asn	Ile	Asn																																
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Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile
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Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp
 835 840 845

Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln
 850 855 860

Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile
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Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr
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Leu Asp

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tccaaaacta aatctctgat agaaggtaga aacaaagcgc tgaacctgca gtgtatcaag	1500
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gagacgtccg aagtatctac taccgacaaa attgcggata tcactatcat catcccgtac	2040
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gacgcctgc tgaaatacat ttacgacaac cgtggcactc tgatcggta ggttgatcgt	2640

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<210> 64

<211> 911

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 64

Leu Gly Ile Glu Gly Arg Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser
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Ala Arg Lys Leu Ala Asn Gln Thr Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Pro Arg Gly Ser Met Glu Phe Val
35 40 45

Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly Val Asp Ile Ala
50 55 60

Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro Val Lys Ala Phe
65 70 75 80

Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg Asp Thr Phe Thr
85 90 95

Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro Pro Glu Ala Lys Gln Val
100 105 110

Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr Asp Asn Glu Lys
115 120 125

Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu Arg Ile Tyr Ser
130 135 140

Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val Arg Gly Ile Pro
145 150 155 160

Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys Val Ile Asp Thr
165 170 175

Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr Arg Ser Glu Glu

180	185	190
Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile Ile Gln Phe Glu		
195	200	205
Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr Arg Asn Gly Tyr		
210	215	220
Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe Thr Phe Gly Phe		
225	230	235
Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu Gly Ala Gly Lys		
245	250	255
Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu Leu Ile His Ala		
260	265	270
Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn Arg Val Phe Lys		
275	280	285
Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu Glu Val Ser Phe		
290	295	300
Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys Phe Ile Asp Ser		
305	310	315
Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn Lys Phe Lys Asp		
325	330	335
Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser Ile Val Gly Thr Thr Ala		
340	345	350
Ser Leu Gln Tyr Met Lys Asn Val Phe Lys Glu Lys Tyr Leu Leu Ser		
355	360	365
Glu Asp Thr Ser Gly Lys Phe Ser Val Asp Lys Leu Lys Phe Asp Lys		
370	375	380
Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr Glu Asp Asn Phe Val Lys		
385	390	395
Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr Leu Asn Phe Asp Lys Ala		
405	410	415
Val Phe Lys Ile Asn Ile Val Pro Lys Val Asn Tyr Thr Ile Tyr Asp		
420	425	430

Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala Ala Asn Phe Asn Gly Gln
 435 440 445

Asn Thr Glu Ile Asn Asn Met Asn Phe Thr Lys Leu Lys Asn Phe Thr
 450 455 460

Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys Val Asp Gly Ile Ile Thr
 465 470 475 480

Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg Asn Lys Ala Leu Asn Leu
 485 490 495

Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu
 500 505 510

Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp
 515 520 525

Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln
 530 535 540

Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser
 545 550 555 560

Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro
 565 570 575

Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr
 580 585 590

Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser
 595 600 605

Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser
 610 615 620

Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys
 625 630 635 640

Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr
 645 650 655

Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala
 660 665 670

Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly
 675 680 685

Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly
 690 695 700

Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu
 705 710 715 720

Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val
 725 730 735

Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu
 740 745 750

Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln
 755 760 765

Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala
 770 775 780

Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu
 785 790 795 800

Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys
 805 810 815

Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu
 820 825 830

Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly
 835 840 845

Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu
 850 855 860

Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg
 865 870 875 880

Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln
 885 890 895

Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
 900 905 910

<210> 65
<211> 177
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

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tttggcggtt tcacggggcg acgcaaatca gcgcgtaaat tagctaacca ggcgctagcg 120
ggtggtggtg gttctgcact agtgctgcag acgcacggtc tagaatgata aaagctt 177

<210> 66
<211> 192
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 66
ggatccacgc acgtcgacgg catcattacc tccaaaacta aatctctgat agaaggtaga 60
tttggcggtt tcacggggcg acgcaaatca gcgcgtaaat tagctaacca ggcgctagcg 120
ggtggtggtg gttctggtgg tgggtggttct gcactagtgc tgcagacgca cggctctagaa 180
tgataaaagc tt 192

<210> 67
<211> 222
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 67
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ggtggtggtg gttctggtgg tgggtggttct ggtggtggtg gttctggtgg tgggtggttct 180
gcactagtgc tgcagacgca cggctctagaa tgataaaagc tt 222

<210> 68
<211> 237
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 68

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 ggtggtggtg gttctggtgg tgggtggttct ggtggtggtg gttctggtgg tgggtggttct 180
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<210> 69
 <211> 228
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 69
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 gctgaagctg ctgctaaaga agctgctgct aaagaagctg ctgctaaagc tgggtggcggt 180
 gggtccgcac tagtgctgca gacgcacggt ctagaatgat aaaagctt 228

<210> 70
 <211> 2694
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 70
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 tactccaccg acctgggccg tatgctgctg actagcatcg ttccggtat cccgttctgg 360
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<210> 71

<211> 897

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 71

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20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
 210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
 245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
 275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
 290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
 305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Leu Ala Asn
450 455 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu
465 470 475 480

Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro
485 490 495

Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr
500 505 510

Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu
515 520 525

Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn
530 535 540

Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu
545 550 555 560

Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp
565 570 575

Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly
580 585 590

Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn
595 600 605

Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val
610 615 620

Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu
625 630 635 640

Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys
645 650 655

Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn
660 665 670

Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe
675 680 685

Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro
690 695 700

Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu
705 710 715 720

Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp
725 730 735

Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn
740 745 750

Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn
755 760 765

Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr
770 775 780

Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser
785 790 795 800

Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys
805 810 815

Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro
820 825 830

Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala
835 840 845

Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val
850 855 860

Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro
865 870 875 880

Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu
885 890 895

Asp

<211> 2724

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 72

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ctgaacattg gcaacatgct gtacaaagac gacttcgttg gcgcactgat cttctccggg 2100
gcggtgatcc tgctggagtt catcccggaa atcgccatcc cggtactggg cacctttgct 2160
ctggtttctt acattgcaaa caaggttctg actgtacaaa ccatcgacaa cgcgctgagc 2220
aaacgtaacg aaaaatggga tgaagtttac aaatatatcg tgaccaactg gctggctaag 2280
gttaatactc agatcgacct catccgcaaa aaaatgaaag aagcactgga aaaccaggcg 2340
gaagctacca aggcaatcat taactaccag tacaaccagt acaccgagga agaaaaaac 2400
aacatcaact tcaacatcga cgatctgtcc tctaaactga acgaatccat caacaaagct 2460
atgatcaaca tcaacaagtt cctgaaccag tgctctgtaa gctatctgat gaactccatg 2520
atcccgtacg gtgttaaacy tctggaggac ttcgatgcgt ctctgaaaga cgccttgctg 2580
aaatacattt acgacaaccg tggcactctg atcggtcagg ttgatcgtct gaaggacaaa 2640
gtgaacaata cttatcgac cgacatccct tttcagctca gtaaatatgt cgataaccaa 2700
cgccttttgt ccactctaga ctag 2724

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<210> 73
 <211> 907
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 73

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
 1 5 10 15

Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
 20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
 35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
 50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
 65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
 85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
 100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
 115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
 130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
 145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
 165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
 180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
 210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
 245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
 275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
 290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
 305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
 435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Leu Ala Asn
 450 455 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
 465 470 475 480

Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys
 485 490 495

Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr
 500 505 510

Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu
 515 520 525

Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu

530		535		540
Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu				
545		550		555 560
Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg				
	565		570	575
Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His				
	580		585	590
Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu				
	595		600	605
Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr				
	610		615	620
Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala				
625		630		635 640
Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp				
	645		650	655
Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile				
	660		665	670
Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr				
	675		680	685
Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu				
	690		695	700
Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala				
705		710		715 720
Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp				
	725		730	735
Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr				
	740		745	750
Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile				
	755		760	765
Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys				
	770		775	780

Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn
785 790 795 800

Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser
805 810 815

Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser
820 825 830

Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu
835 840 845

Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr
850 855 860

Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys
865 870 875 880

Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr
885 890 895

Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
900 905

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<211> 207
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 74
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tttggcgggtt tcacggggcgc acgcaaatac gcgcgtaaac gtaagaacca ggcgctagcg 120
ggcgggtggcg gtagcggcgg tggcggtagc ggcgggtggcg gtagcgcact agtgctgcag 180
acgcacgggtc tagaatgata aaagctt 207

<210> 75
<211> 2709
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 75

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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaaccgga agaaggtgac	180
ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg	240
tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactggt cgagcgtatt	300
tactccaccg acctgggccc tatgctgctg actagcatcg ttccggttat cccgttctgg	360
ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt	420
cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct	480
gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct caccgtaac	540
ggctacgggt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa	600
tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg	660
gttaccctgg ctacgaact gattcatgca ggccaccgcc tgtacgggat cgccatcaat	720
ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt	780
agcttcgaag aactgcgtac ttttggcggc caccgacgta aattcatcga ctctctgcaa	840
gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac	900
aaagcgaaat ccatcgtagg taccactgct tctctccagt acatgaagaa cgtttttaa	960
gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc	1020
gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt	1080
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gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct	1200
gctaatttta acggccagaa caccgaaatc aacaacatga acttcacaaa actgaaaaac	1260
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actaaatctg acgatgacga taaatttggc ggtttcacgg gcgcacgcaa atcagcgcgt	1380
aaacgtaaga accaggcgct agcgggaggc ggcggttagc gcggtggcgg tagcggcggt	1440
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aacatcgaag cagccgaaga aaacatctcg ctggacctga tccagcagta ctacctgacc	1620
tttaatttcg acaacgagcc ggaaaacatt tctatcgaaa acctgagctc tgatatcatc	1680
ggccagctgg aactgatgcc gaacatcgaa cgtttcccaa acggtaaaaa gtacgagctg	1740
gacaaatata ccatgttcca ctacctgcgc gcgcaggaat ttgaacacgg caaatcccgt	1800
atcgactga ctaactccgt taacgaagct ctgctcaacc cgtcccgtgt atacaccttc	1860


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tgsggtgaac agcttggtta tgatgttacc gacgagacgt ccgaagtatc tactaccgac 1980
aaaattgcgg atatcactat catcatcccg tacatcggtc cggctctgaa cattggcaac 2040
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gagttcatcc cggaatcgc catcccggtg ctgggcacct ttgctctggt ttcttacatt 2160
gcaaacaagg ttctgactgt acaaaccatc gacaacgcgc tgagcaaacg taacgaaaaa 2220
tgsgatgaag ttacaaata tatcgtgacc aactggctgg ctaagggtta tactcagatc 2280
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atcgacgatc tgtctctaa actgaacgaa tccatcaaca aagctatgat caacatcaac 2460
aagttcctga accagtgtc tgtaagctat ctgatgaact ccatgatccc gtacggtgtt 2520
aaacgtctgg aggacttga tgcgtctctg aaagacgccc tgctgaaata catttacgac 2580
aaccgtggca ctctgatcg tcaggttgat cgtctgaagg acaaagtga caatacctta 2640
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ctagactag 2709

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<210> 76
<211> 902
<212> PRT
<213> Artificial Sequence

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<220>
<223> Synthetic

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<400> 76

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Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
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```

```

Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
          20           25           30

```

```

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35           40           45

```

```

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50           55           60

```

```

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65           70           75           80

```

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Asp Asp Asp Asp Lys
 435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys Asn
 450 455 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly
 465 470 475 480

Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp
 485 490 495

Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys
 500 505 510

Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn
 515 520 525

Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp
 530 535 540

Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile
 545 550 555 560

Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys

565					570					575					
Lys	Tyr	Glu	Leu	Asp	Lys	Tyr	Thr	Met	Phe	His	Tyr	Leu	Arg	Ala	Gln
		580						585					590		
Glu	Phe	Glu	His	Gly	Lys	Ser	Arg	Ile	Ala	Leu	Thr	Asn	Ser	Val	Asn
		595					600					605			
Glu	Ala	Leu	Leu	Asn	Pro	Ser	Arg	Val	Tyr	Thr	Phe	Phe	Ser	Ser	Asp
	610					615					620				
Tyr	Val	Lys	Lys	Val	Asn	Lys	Ala	Thr	Glu	Ala	Ala	Met	Phe	Leu	Gly
625					630					635					640
Trp	Val	Glu	Gln	Leu	Val	Tyr	Asp	Phe	Thr	Asp	Glu	Thr	Ser	Glu	Val
				645					650					655	
Ser	Thr	Thr	Asp	Lys	Ile	Ala	Asp	Ile	Thr	Ile	Ile	Ile	Pro	Tyr	Ile
			660					665					670		
Gly	Pro	Ala	Leu	Asn	Ile	Gly	Asn	Met	Leu	Tyr	Lys	Asp	Asp	Phe	Val
		675					680					685			
Gly	Ala	Leu	Ile	Phe	Ser	Gly	Ala	Val	Ile	Leu	Leu	Glu	Phe	Ile	Pro
	690					695					700				
Glu	Ile	Ala	Ile	Pro	Val	Leu	Gly	Thr	Phe	Ala	Leu	Val	Ser	Tyr	Ile
705					710					715					720
Ala	Asn	Lys	Val	Leu	Thr	Val	Gln	Thr	Ile	Asp	Asn	Ala	Leu	Ser	Lys
				725					730					735	
Arg	Asn	Glu	Lys	Trp	Asp	Glu	Val	Tyr	Lys	Tyr	Ile	Val	Thr	Asn	Trp
			740					745					750		
Leu	Ala	Lys	Val	Asn	Thr	Gln	Ile	Asp	Leu	Ile	Arg	Lys	Lys	Met	Lys
		755					760					765			
Glu	Ala	Leu	Glu	Asn	Gln	Ala	Glu	Ala	Thr	Lys	Ala	Ile	Ile	Asn	Tyr
	770					775					780				
Gln	Tyr	Asn	Gln	Tyr	Thr	Glu	Glu	Glu	Lys	Asn	Asn	Ile	Asn	Phe	Asn
785					790					795					800
Ile	Asp	Asp	Leu	Ser	Ser	Lys	Leu	Asn	Glu	Ser	Ile	Asn	Lys	Ala	Met
				805					810					815	

Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
 820 825 830

Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
 835 840 845

Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
 850 855 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
 865 870 875 880

Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg
 885 890 895

Leu Leu Ser Thr Leu Asp
 900

<210> 77
 <211> 207
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 77
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 ggcggtggcg gtagcggcgg tggcggtagc ggcggtggcg gtagcgact agtgctgcag 180
 acgcacggtc tagaatgata aaagctt 207

<210> 78
 <211> 2742
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 78
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 aaaaacatcc tgtacctgga taccatctg aataccctgg cgaacgaacc ggaaaaagcg 120
 tttcgatatca ccggcaacat ttgggttatt ccggtcgtt ttagccgtaa cagcaaccgc 180
 aatctgaata aacggcgcgg tgtaccagc ccgaaaagcg gttattacga tccgaactat 240

ctgagcaccg atagcgataa agataccttc ctgaaagaaa tcatcaaact gttcaaacgc	300
atcaacagcc gtgaaattgg cgaagaactg atctatcgcc tgagcaccga tattccgttt	360
ccgggcaaca acaacacccc gatcaacacc tttgatttcg atgtggattt caacagcggt	420
gatgttaaaa cccgccaggg taacaattgg gtgaaaaccg gcagcattaa cccgagcggt	480
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ctgaacatta gcaatagcgt gcgtcgtggc aattttaccg aagcgtttgc ggttaccggt	2100

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 aacctgatcg atagccacaa cattattctg gtgggcgaag tggataaact gaaagcgaaa 2640
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<210> 79
 <211> 913
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 79

Gly Ser Glu Phe Met Pro Ile Thr Ile Asn Asn Phe Asn Tyr Ser Asp
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Pro Val Asp Asn Lys Asn Ile Leu Tyr Leu Asp Thr His Leu Asn Thr
 20 25 30

Leu Ala Asn Glu Pro Glu Lys Ala Phe Arg Ile Thr Gly Asn Ile Trp
 35 40 45

Val Ile Pro Asp Arg Phe Ser Arg Asn Ser Asn Pro Asn Leu Asn Lys
 50 55 60

Pro Pro Arg Val Thr Ser Pro Lys Ser Gly Tyr Tyr Asp Pro Asn Tyr
 65 70 75 80

Leu Ser Thr Asp Ser Asp Lys Asp Thr Phe Leu Lys Glu Ile Ile Lys
 85 90 95

Leu Phe Lys Arg Ile Asn Ser Arg Glu Ile Gly Glu Glu Leu Ile Tyr

105 110

Arg Leu Ser Thr Asp Ile Pro Phe Pro Gly Asn Asn Asn Thr Pro Ile
 115 120 125

Asn Thr Phe Asp Phe Asp Val Asp Phe Asn Ser Val Asp Val Lys Thr
 130 135 140

Arg Gln Gly Asn Asn Trp Val Lys Thr Gly Ser Ile Asn Pro Ser Val
 145 150 155 160

Ile Ile Thr Gly Pro Arg Glu Asn Ile Ile Asp Pro Glu Thr Ser Thr
 165 170 175

Phe Lys Leu Thr Asn Asn Thr Phe Ala Ala Gln Glu Gly Phe Gly Ala
 180 185 190

Leu Ser Ile Ile Ser Ile Ser Pro Arg Phe Met Leu Thr Tyr Ser Asn
 195 200 205

Ala Thr Asn Asp Val Gly Glu Gly Arg Phe Ser Lys Ser Glu Phe Cys
 210 215 220

Met Asp Pro Ile Leu Ile Leu Met His Glu Leu Asn His Ala Met His
 225 230 235 240

Asn Leu Tyr Gly Ile Ala Ile Pro Asn Asp Gln Thr Ile Ser Ser Val
 245 250 255

Thr Ser Asn Ile Phe Tyr Ser Gln Tyr Asn Val Lys Leu Glu Tyr Ala
 260 265 270

Glu Ile Tyr Ala Phe Gly Gly Pro Thr Ile Asp Leu Ile Pro Lys Ser
 275 280 285

Ala Arg Lys Tyr Phe Glu Glu Lys Ala Leu Asp Tyr Tyr Arg Ser Ile
 290 295 300

Ala Lys Arg Leu Asn Ser Ile Thr Thr Ala Asn Pro Ser Ser Phe Asn
 305 310 315 320

Lys Tyr Ile Gly Glu Tyr Lys Gln Lys Leu Ile Arg Lys Tyr Arg Phe
 325 330 335

Val Val Glu Ser Ser Gly Glu Val Thr Val Asn Arg Asn Lys Phe Val
 340 345 350

Glu Leu Tyr Asn Glu Leu Thr Gln Ile Phe Thr Glu Phe Asn Tyr Ala
 355 360 365

Lys Ile Tyr Asn Val Gln Asn Arg Lys Ile Tyr Leu Ser Asn Val Tyr
 370 375 380

Thr Pro Val Thr Ala Asn Ile Leu Asp Asp Asn Val Tyr Asp Ile Gln
 385 390 395 400

Asn Gly Phe Asn Ile Pro Lys Ser Asn Leu Asn Val Leu Phe Met Gly
 405 410 415

Gln Asn Leu Ser Arg Asn Pro Ala Leu Arg Lys Val Asn Pro Glu Asn
 420 425 430

Met Leu Tyr Leu Phe Thr Lys Phe Cys Val Asp Gly Ile Ile Thr Ser
 435 440 445

Lys Thr Lys Ser Leu Ile Glu Gly Arg Phe Gly Gly Phe Thr Gly Ala
 450 455 460

Arg Lys Ser Ala Arg Lys Arg Lys Asn Gln Ala Leu Ala Gly Gly Gly
 465 470 475 480

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu
 485 490 495

Gln Cys Arg Glu Leu Leu Val Lys Asn Thr Asp Leu Pro Phe Ile Gly
 500 505 510

Asp Ile Ser Asp Val Lys Thr Asp Ile Phe Leu Arg Lys Asp Ile Asn
 515 520 525

Glu Glu Thr Glu Val Ile Tyr Tyr Pro Asp Asn Val Ser Val Asp Gln
 530 535 540

Val Ile Leu Ser Lys Asn Thr Ser Glu His Gly Gln Leu Asp Leu Leu
 545 550 555 560

Tyr Pro Ser Ile Asp Ser Glu Ser Glu Ile Leu Pro Gly Glu Asn Gln
 565 570 575

Val Phe Tyr Asp Asn Arg Thr Gln Asn Val Asp Tyr Leu Asn Ser Tyr
 580 585 590

Tyr Tyr Leu Glu Ser Gln Lys Leu Ser Asp Asn Val Glu Asp Phe Thr

595	600	605
Phe Thr Arg Ser Ile Glu Glu Ala Leu Asp Asn Ser Ala Lys Val Tyr 610 615 620		
Thr Tyr Phe Pro Thr Leu Ala Asn Lys Val Asn Ala Gly Val Gln Gly 625 630 635 640		
Gly Leu Phe Leu Met Trp Ala Asn Asp Val Val Glu Asp Phe Thr Thr 645 650 655		
Asn Ile Leu Arg Lys Asp Thr Leu Asp Lys Ile Ser Asp Val Ser Ala 660 665 670		
Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Ser Asn Ser Val Arg 675 680 685		
Arg Gly Asn Phe Thr Glu Ala Phe Ala Val Thr Gly Val Thr Ile Leu 690 695 700		
Leu Glu Ala Phe Pro Glu Phe Thr Ile Pro Ala Leu Gly Ala Phe Val 705 710 715 720		
Ile Tyr Ser Lys Val Gln Glu Arg Asn Glu Ile Ile Lys Thr Ile Asp 725 730 735		
Asn Cys Leu Glu Gln Arg Ile Lys Arg Trp Lys Asp Ser Tyr Glu Trp 740 745 750		
Met Met Gly Thr Trp Leu Ser Arg Ile Ile Thr Gln Phe Asn Asn Ile 755 760 765		
Ser Tyr Gln Met Tyr Asp Ser Leu Asn Tyr Gln Ala Gly Ala Ile Lys 770 775 780		
Ala Lys Ile Asp Leu Glu Tyr Lys Lys Tyr Ser Gly Ser Asp Lys Glu 785 790 795 800		
Asn Ile Lys Ser Gln Val Glu Asn Leu Lys Asn Ser Leu Asp Val Lys 805 810 815		
Ile Ser Glu Ala Met Asn Asn Ile Asn Lys Phe Ile Arg Glu Cys Ser 820 825 830		
Val Thr Tyr Leu Phe Lys Asn Met Leu Pro Lys Val Ile Asp Glu Leu 835 840 845		

Asn Glu Phe Asp Arg Asn Thr Lys Ala Lys Leu Ile Asn Leu Ile Asp
 850 855 860

Ser His Asn Ile Ile Leu Val Gly Glu Val Asp Lys Leu Lys Ala Lys
 865 870 875 880

Val Asn Asn Ser Phe Gln Asn Thr Ile Pro Phe Asn Ile Phe Ser Tyr
 885 890 895

Thr Asn Asn Ser Leu Leu Lys Asp Ile Ile Asn Glu Tyr Phe Asn Leu
 900 905 910

Asp

<210> 80
 <211> 2673
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 80
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 cacaacaaaa tctgggttat cccggaacgt gataccttta ctaaccgga agaaggtgac 180
 ctgaaccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240
 tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300
 tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360
 ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420
 cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480
 gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540
 ggctacgggt ccaactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600
 tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660
 gttacctggt ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720
 ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780
 agcttcgaag aactgcgtac ttttgccggt caccgacgta aattcatcga ctctctgcaa 840
 gaaaacgagt tccgtctgta ctactataac aagttcaaaag atatcgcatc caccctgaac 900

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gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020
gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080
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gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200
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aacaagcta tgatcaacat caacaagttc ctgaaccagt gctctgtaag ctatctgatg 2460
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gccctgctga aatacattta cgacaaccgt ggcaactctga tcggtcaggt tgatcgtctg 2580
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gataaccaac gccttttctc cactctagac tag 2673

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<210> 81
 <211> 890
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 81

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
 20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
 35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
 50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
 65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
 85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
 100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
 115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
 130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
 145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
 165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
 180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
 210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
 245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
 275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
 290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
 305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
 435 440 445

Tyr Gly Gly Phe Leu Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly
 450 455 460

Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val
 465 470 475 480

Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn
 485 490 495

Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala
 500 505 510

Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr
 515 520 525

Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser
 530 535 540

Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe
 545 550 555 560

Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr
 565 570 575

Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr
 580 585 590

Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe
 595 600 605

Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala
 610 615 620

Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu
 625 630 635 640

Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile
 645 650 655

Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys
 660 665 670

Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu
 675 680 685

Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu

690	695	700
Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn		
705	710	715 720
Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile		
	725	730 735
Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg		
	740	745 750
Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala		
	755	760 765
Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn		
	770	775 780
Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile		
	785	790 795 800
Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val		
	805	810 815
Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu		
	820	825 830
Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp		
	835	840 845
Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val		
	850	855 860
Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val		
	865	870 875 880
Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp		
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<210> 82

<211> 2709

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 82

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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaaccgga agaaggtgac	180
ctgaaccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg	240
tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt	300
tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg	360
ggcgggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt	420
cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct	480
gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct caccgtaac	540
ggctacggtt ccaactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa	600
tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg	660
gttaccctgg ctacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat	720
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agcttcgaag aactgcgtac ttttggcggc caccgacgta aattcatcga ctctctgcaa	840
gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac	900
aaagcgaaat ccatcgtagg taccactgct tctctccagt acatgaagaa cgttttttaa	960
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gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt	1080
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gacaaatata ccatgttcca ctacctgcgc gcgcaggaat ttgaacacgg caaatcccgt	1800
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atcgacgatc tgtcctctaa actgaacgaa tccatcaaca aagctatgat caacatcaac 2460
aagttcctga accagtgctc tgtaagctat ctgatgaact ccatgatccc gtacggtggt 2520
aaacgtctgg aggacttcga tgcgtctctg aaagacgccc tgctgaaata catttacgac 2580
aaccgtggca ctctgatcgg tcaggttgat cgtctgaagg acaaagtgaa caatacctta 2640
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ctagactag 2709

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<210> 83
 <211> 902
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 83

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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
          20           25           30

```

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Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
          35           40           45

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Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
          50           55           60

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Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65           70           75           80

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Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp

325	330	335
Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr 340 345 350		
Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr 355 360 365		
Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val 370 375 380		
Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala 385 390 395 400		
Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr 405 410 415		
Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys 420 425 430		
Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg 435 440 445		
Tyr Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Leu Ala Asn 450 455 460		
Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly 465 470 475 480		
Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp 485 490 495		
Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys 500 505 510		
Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn 515 520 525		
Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp 530 535 540		
Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile 545 550 555 560		
Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys 565 570 575		

Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln
580 585 590

Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn
595 600 605

Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp
610 615 620

Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly
625 630 635 640

Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val
645 650 655

Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile
660 665 670

Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val
675 680 685

Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro
690 695 700

Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile
705 710 715 720

Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys
725 730 735

Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp
740 745 750

Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys
755 760 765

Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr
770 775 780

Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn
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Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
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Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
 835 840 845

Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
 850 855 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
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Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
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Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
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Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
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His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
 245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
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Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
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Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
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Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
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Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
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Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
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Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
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Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
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Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
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Tyr Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys Asn
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Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile
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Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys
 565 570 575

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Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp
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Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr
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Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn
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Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met
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Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
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Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
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Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
 850 855 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
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<213> Artificial Sequence

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<220>
<223> Synthetic

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```

<400> 88

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Gly Ser Leu Val Arg Asp Asp Val Asp Tyr Gln Ile Phe Arg Asp Phe
1           5           10           15

```

```

Ala Glu Asn Lys Gly Lys Phe Phe Val Gly Ala Thr Asp Leu Ser Val
          20           25           30

```

```

Lys Asn Lys Arg Gly Gln Asn Ile Gly Asn Ala Leu Ser Asn Val Pro
          35           40           45

```

```

Met Ile Asp Phe Ser Val Ala Asp Val Asn Lys Arg Ile Ala Thr Val
          50           55           60

```

```

Val Asp Pro Gln Tyr Ala Val Ser Val Lys His Ala Lys Ala Glu Val
65           70           75           80

```

```

His Thr Phe Tyr Tyr Gly Gln Tyr Asn Gly His Asn Asp Val Ala Asp
          85           90           95

```

```

Lys Glu Asn Glu Tyr Arg Val Val Glu Gln Asn Asn Tyr Glu Pro His
          100          105          110

```

```

Lys Ala Trp Gly Ala Ser Asn Leu Gly Arg Leu Glu Asp Tyr Asn Met
          115          120          125

```

```

Ala Arg Phe Asn Lys Phe Val Thr Glu Val Ala Pro Ile Ala Pro Thr
          130          135          140

```


Asp Ala Gly Gly Gly Leu Asp Thr Tyr Lys Asp Lys Asn Arg Phe Ser
145 150 155 160

Ser Phe Val Arg Ile Gly Ala Gly Arg Gln Leu Val Tyr Glu Lys Gly
165 170 175

Val Tyr His Gln Glu Gly Asn Glu Lys Gly Tyr Asp Leu Arg Asp Leu
180 185 190

Ser Gln Ala Tyr Arg Tyr Ala Ile Ala Gly Thr Pro Tyr Lys Asp Ile
195 200 205

Asn Ile Asp Gln Thr Met Asn Thr Glu Gly Leu Ile Gly Phe Gly Asn
210 215 220

His Asn Lys Gln Tyr Ser Ala Glu Glu Leu Lys Gln Ala Leu Ser Gln
225 230 235 240

Asp Ala Leu Thr Asn Tyr Gly Val Leu Gly Asp Ser Gly Ser Pro Leu
245 250 255

Phe Ala Phe Asp Lys Gln Lys Asn Gln Trp Val Phe Leu Gly Thr Tyr
260 265 270

Asp Tyr Trp Ala Gly Tyr Gly Lys Lys Ser Trp Gln Glu Trp Asn Ile
275 280 285

Tyr Lys Lys Glu Phe Ala Asp Lys Ile Lys Gln His Asp Asn Ala Gly
290 295 300

Thr Val Lys Gly Asn Gly Glu His His Trp Lys Thr Thr Gly Thr Asn
305 310 315 320

Ser His Ile Gly Ser Thr Ala Val Arg Leu Ala Asn Asn Glu Gly Asp
325 330 335

Ala Asn Asn Gly Gln Asn Val Thr Phe Glu Asp Asn Gly Thr Leu Val
340 345 350

Leu Asn Gln Asn Ile Asn Gln Gly Ala Gly Gly Leu Phe Phe Lys Gly
355 360 365

Asp Tyr Thr Val Lys Gly Ala Asn Asn Asp Ile Thr Trp Leu Gly Ala
370 375 380

Gly Ile Asp Val Ala Asp Gly Lys Lys Val Val Trp Gln Val Lys Asn
 385 390 395 400

Pro Asn Gly Asp Arg Leu Ala Lys Ile Gly Lys Gly Thr Leu Glu Ile
 405 410 415

Asn Gly Thr Gly Val Asn Gln Gly Gln Leu Lys Val Gly Asp Gly Thr
 420 425 430

Val Ile Leu Asn Gln Lys Ala Asp Ala Asp Lys Lys Val Gln Ala Phe
 435 440 445

Ser Gln Val Gly Ile Val Ser Gly Arg Gly Thr Leu Val Leu Asn Ser
 450 455 460

Ser Asn Gln Ile Asn Pro Asp Asn Leu Tyr Phe Gly Phe Arg Gly Gly
 465 470 475 480

Arg Leu Asp Ala Asn Gly Asn Asp Leu Thr Phe Glu His Ile Arg Asn
 485 490 495

Val Asp Glu Gly Ala Arg Ile Val Asn His Asn Thr Asp His Ala Ser
 500 505 510

Thr Ile Thr Leu Thr Gly Lys Ser Leu Ile Thr Asn Pro Asn Ser Leu
 515 520 525

Ser Val His Ser Ile Gln Asn Asp Tyr Asp Glu Asp Asp Tyr Ser Tyr
 530 535 540

Tyr Tyr Arg Pro Arg Arg Pro Ile Pro Gln Gly Lys Asp Leu Tyr Tyr
 545 550 555 560

Lys Asn Tyr Arg Tyr Tyr Ala Leu Lys Ser Gly Gly Arg Leu Asn Ala
 565 570 575

Pro Met Pro Glu Asn Gly Val Ala Glu Asn Asn Asp Trp Ile Phe Met
 580 585 590

Gly Tyr Thr Gln Glu Glu Ala Arg Lys Asn Ala Met Asn His Lys Asn
 595 600 605

Asn Arg Arg Ile Gly Asp Phe Gly Gly Phe Phe Asp Glu Glu Asn Gly
 610 615 620

Lys Gly His Asn Gly Ala Leu Asn Leu Asn Phe Asn Gly Lys Ser Ala
625 630 635 640

Gln Lys Arg Phe Leu Leu Thr Gly Gly Ala Asn Leu Asn Gly Lys Ile
645 650 655

Ser Val Thr Gln Gly Asn Val Leu Leu Ser Gly Arg Pro Thr Pro His
660 665 670

Ala Arg Asp Phe Val Asn Lys Ser Ser Ala Arg Lys Asp Ala His Phe
675 680 685

Ser Lys Asn Asn Glu Val Val Phe Glu Asp Asp Trp Ile Asn Arg Thr
690 695 700

Phe Lys Ala Ala Glu Ile Ala Val Asn Gln Ser Ala Ser Phe Ser Ser
705 710 715 720

Gly Arg Asn Val Ser Asp Ile Thr Ala Asn Ile Thr Ala Thr Asp Asn
725 730 735

Ala Lys Val Asn Leu Gly Tyr Lys Asn Gly Asp Glu Val Cys Val Arg
740 745 750

Ser Asp Tyr Thr Gly Tyr Val Thr Cys Asn Thr Gly Asn Leu Ser Asp
755 760 765

Lys Ala Leu Asn Ser Phe Asp Ala Thr Arg Ile Asn Gly Asn Val Asn
770 775 780

Leu Asn Gln Asn Ala Ala Leu Val Leu Gly Lys Ala Ala Leu Trp Gly
785 790 795 800

Lys Ile Gln Gly Gln Gly Asn Ser Arg Val Ser Leu Asn Gln His Ser
805 810 815

Lys Trp His Leu Thr Gly Asp Ser Gln Val His Asn Leu Ser Leu Ala
820 825 830

Asp Ser His Ile His Leu Asn Asn Ala Ser Asp Ala Gln Ser Ala Asn
835 840 845

Lys Tyr His Thr Ile Lys Ile Asn His Leu Ser Gly Asn Gly His Phe
850 855 860

His Tyr Leu Thr Asp Leu Ala Lys Asn Leu Gly Asp Lys Val Leu Val

865	870	875	880
Lys Glu Ser Ala Ser Gly His Tyr Gln Leu His Val Gln Asn Lys Thr	885	890	895
Gly Glu Pro Asn Gln Glu Gly Leu Asp Leu Phe Asp Ala Ser Ser Val	900	905	910
Gln Asp Arg Ser Arg Leu Phe Val Ser Leu Ala Asn His Tyr Val Asp	915	920	925
Leu Gly Ala Leu Arg Tyr Thr Ile Lys Thr Glu Asn Gly Ile Thr Arg	930	935	940
Leu Tyr Asn Pro Tyr Ala Gly Asn Gly Arg Pro Val Lys Pro Ala Pro	945	950	955
Cys Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly	965	970	975
Arg Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys	980	985	990
Asn Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly	995	1000	1005
Gly Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn	1010	1015	1020
Trp Asp Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp	1025	1030	1035
Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala	1040	1045	1050
Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu	1055	1060	1065
Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn	1070	1075	1080
Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro Asn Ile	1085	1090	1095
Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr Thr	1100	1105	1110

Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser
1115 1120 1125

Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro
1130 1135 1140

Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val
1145 1150 1155

Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln
1160 1165 1170

Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr
1175 1180 1185

Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro
1190 1195 1200

Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly
1205 1210 1215

Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro
1220 1225 1230

Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr
1235 1240 1245

Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu
1250 1255 1260

Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val
1265 1270 1275

Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg
1280 1285 1290

Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys
1295 1300 1305

Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys
1310 1315 1320

Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn
1325 1330 1335

Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn
1340 1345 1350

Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly
1355 1360 1365

Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu
1370 1375 1380

Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val
1385 1390 1395

Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile
1400 1405 1410

Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser
1415 1420 1425

Thr Leu Asp
1430

<210> 89
<211> 1357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 89
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gctgcagtgt atcaaggta acaactggga tttattcttc agcccgagtg aagacaactt 120
caccaacgac ctgaacaaag gtgaagaaat cacctcagat actaacatcg aagcagccga 180
agaaaacatc tcgctggacc tgatccagca gtactacctg acctttaatt tcgacaacga 240
gccggaaaac atttctatcg aaaacctgag ctctgatatc atcggccagc tggaactgat 300
gccgaacatc gaacgtttcc caaacggtaa aaagtacgag ctggacaaat ataccatgtt 360
ccactacctg cgcgcgcagg aatttgaaca cggcaaatec cgtatcgcac tgactaactc 420
cgttaacgaa gctctgctca acccggtccc tggtatacacc ttcttctcta gcgactacgt 480
gaaaaaggta aacaaagcga ctgaagctgc aatgttcttg ggttgggttg aacagcttgt 540
ttatgatttt accgacgaga cgtccgaagt atctactacc gacaaaattg cggatatcac 600
tatcatcatc ccgtacatcg gtccggctct gaacattggc aacatgctgt acaaagacga 660
cttcgttggc gcactgatct tctccggtgc ggtgatctg ctggagttca tcccggaaat 720

cgccatcccg gtactgggca cctttgctct ggtttcttac attgcaaaca aggttctgac 780
 tgtacaaacc atcgacaacg cgctgagcaa acgtaacgaa aaatgggatg aagttttacaa 840
 atatatcgtg accaactggc tggctaaggt taatactcag atcgacctca tccgcaaaaa 900
 aatgaaagaa gcactggaaa accaggcgga agctaccaag gcaatcatta actaccagta 960
 caaccagtac accgaggaag aaaaaaacia catcaacttc aacatcgacg atctgtcctc 1020
 taaactgaac gaatccatca acaaagctat gatcaacatc aacaagttcc tgaaccagtg 1080
 ctctgtaagc tatctgatga actccatgat cccgtacggg gttaaactgc tggaggactt 1140
 cgatgcgtct ctgaaagacg ccttgctgaa atacatttac gacaaccgtg gcactctgat 1200
 cggtcagggt gatcgtctga aggacaaagt gaacaatacc ttatcgaccg acatcccttt 1260
 tcagctcagt aaatatgtcg ataaccaacg ccttttgtcc actctagaaa tagaaggtag 1320
 aagtgggcac catcaccatc accattaatg aaagctt 1357

<210> 90
 <211> 2745
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 90
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 attgcttaca tcaaaatccc gaacgctggc cagatgcagc cggtaaaggc attcaaaatc 120
 cacaacaaaa tctgggttat cccggaacgt gataccttta ctaaccgga agaaggtgac 180
 ctgaaccgc caccggaagc gaaacagggt cgggtatctt actatgactc cacctacctg 240
 tctaccgata acgaaaagga caactacctg aaagggtgta ctaaactgtt cgagcgtatt 300
 tactccaccg acctgggccc tatgctgctg actagcatcg ttcgcgggat cccgttctgg 360
 ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420
 cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480
 gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct caccgtaac 540
 ggctacgggt ccaactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600
 tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660
 gttaccctgg ctacgaact gattcatgca ggccaccgcc tgtacgggat cgccatcaat 720
 ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780
 agcttcgaag aactgcgtac ttttggcggg cagcagcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac	900
aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa	960
gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc	1020
gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt	1080
aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc	1140
gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctgggt	1200
gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac	1260
ttcactggtc tgttcgagtt ttacaagctg ctgtgcgtcg acggcatcat tacctccaaa	1320
actaaatctc tgatagaagg tagatttggc ggtttcacgg gcgcacgcaa atcagcgcgt	1380
aaacgtaaga accaggcgct agcggggcgg ggcggtagcg gcggtggcgg tagcggcggt	1440
ggcggtagcg cactagtgtc gcagtgtatc aaggttaaca actgggatctt attcttcagc	1500
ccgagtgaag acaacttcac caacgacctg aacaaagggtg aagaaatcac ctgagatact	1560
aacatcgaag cagccgaaga aaacatctcg ctggacctga tccagcagta ctacctgacc	1620
tttaatttcg acaacgagcc ggaaaacatt tctatcgaaa acctgagctc tgatatcatc	1680
ggccagctgg aactgatgcc gaacatcgaa cgtttcccaa acggtaaaaa gtacgagctg	1740
gacaaatata ccatgttcca ctacctgcgc gcgcaggaat ttgaacacgg caaatcccgt	1800
atcgcaactga ctaactccgt taacgaagct ctgctcaacc cgtcccgtgt atacaccttc	1860
ttctctagcg actacgtgaa aaagggtcaac aaagcgactg aagctgcaat gttcttgggt	1920
tgggttgaac agcttgttta tgattttacc gacgagacgt ccgaagtatc tactaccgac	1980
aaaattgcgg atatcactat catcatcccg tacatcggtc cggctctgaa cattggcaac	2040
atgctgtaca aagacgactt cgttggcgca ctgatcttct ccggtgcggg gatcctgctg	2100
gagttcatcc cggaaatcgc catcccggtg ctgggcacct ttgctctggg ttcttacatt	2160
gcaaacaagg ttctgactgt acaaaccatc gacaacgcgc tgagcaaacg taacgaaaaa	2220
tgggatgaag ttacaaata tatcgtgacc aactggctgg ctaagggttaa tactcagatc	2280
gacctcatcc gcaaaaaaat gaaagaagca ctggaaaacc aggcggaagc taccaaggca	2340
atcattaact accagtacaa ccagtaacac gaggaagaaa aaaacaacat caacttcaac	2400
atcgacgatc tgcctcttaa actgaacgaa tccatcaaca aagctatgat caacatcaac	2460
aagttcctga accagtgtc tgtaagctat ctgatgaact ccatgatccc gtacggtggt	2520
aaacgtctgg aggacttcga tgcgtctctg aaagacgccc tgctgaaata catttacgac	2580
aacggtggca ctctgatcgg tcaggttgat cgtctgaagg acaagtgaa caatacctta	2640
tcgaccgaca tcccttttca gctcagtaaa tatgtcgata accaacgcct tttgtccact	2700

ctagaaatag aaggtagaag tgggcacccat caccatcacc attaa

2745

<210> 91
 <211> 914
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 91

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
 1 5 10 15

Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
 20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
 35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
 50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
 65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
 85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
 100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
 115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
 130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
 145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
 165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
 180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
 195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
 210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
 225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
 245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
 275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
 290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
 305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
 435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys Asn
 450 455 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
 465 470 475 480

Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp
 485 490 495

Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys
 500 505 510

Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn
 515 520 525

Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp
 530 535 540

Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile
 545 550 555 560

Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys
 565 570 575

Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln
 580 585 590

Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn
 595 600 605

Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp
 610 615 620

Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly
 625 630 635 640

Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val
 645 650 655

Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile
 660 665 670

Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val

675	680	685
Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro		
690	695	700
Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile		
705	710	715 720
Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys		
	725	730 735
Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp		
	740	745 750
Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys		
	755	760 765
Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr		
	770	775 780
Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn		
785	790	795 800
Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met		
	805	810 815
Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met		
	820	825 830
Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala		
	835	840 845
Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr		
850	855	860
Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu		
865	870	875 880
Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg		
	885	890 895
Leu Leu Ser Thr Leu Glu Ile Glu Gly Arg Ser Gly His His His His		
	900	905 910
His His		

<210> 92
 <211> 619
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 92
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 gtctttgaaa gaacacggcc cgatcaaaaa taagatgtct gaatcaccca ataaaactgt 180
 ttcggaggaa aaagcgaaac agtattttgga agagtttcat caaacccgcg ttgaacatcc 240
 ggagctcagt gaactgaaaa cagtgcgggg aacgaatcct gtttttgcag gcgcaaacta 300
 tgcggcttgg gccgtgaatg ttgccaagt aattgatagt gagaccgcag acaacctgga 360
 aaagacgacc gcagcgtaa gcattttacc ggggattggg tccgtgatgg gtatagcgga 420
 tggagcggtc caccataaca ctgaggaaat tgtcgccag tcaatcgctc tgagttccct 480
 gatggttgca caggctatcc cactcgtggg ggaactggtt gacatagggt tcgccgccta 540
 caacttcgta gaaagcatta ttaatctttt tcagggtgtg cataacagct acaaccgccc 600
 tctagaatga taaaagctt 619

<210> 93
 <211> 1971
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 93
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 attgcttaca tcaaaaatccc gaacgctggc cagatgcagc cggtaaaggc attcaaaatc 120
 cacaacaaaa tctgggttat cccggaacgt gataccttta ctaaccgga agaaggtgac 180
 ctgaaccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240
 tctaccgata acgaaaagga caactacctg aaagggtgta ctaaactgtt cgagcgtatt 300
 tactccaccg acctgggccc tatgctgctg actagcatcg ttcgcggat cccgttctgg 360
 ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420
 cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480
 gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct caccgtaac 540

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ggctacgggt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600
tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660
gttaccctgg ctacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720
ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780
agcttcgaag aactgcgtac ttttggcggc cacgacgcta aattcatcga ctctctgcaa 840
gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900
aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgttttttaa 960
gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020
gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080
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gattgggacg taatccgtga taagacaaa acaaaaatcg agtctttgaa agaacacggc 1500
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cagtatttgg aagagtttca tcaaaccgcg cttgaacatc cggagctcag tgaactgaaa 1620
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gttgcccaag taattgatag tgagaccgca gacaacctgg aaaagacgac cgcagcgtaa 1740
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actgaggaaa ttgtcgccca gtcaatcgct ctgagttccc tgatggttgc acaggctatc 1860
ccactcgtgg gggaactggg tgacataggt ttcgccgcct acaacttcgt agaaagcatt 1920
attaatcttt ttcagtggt gcataacagc tacaaccgcc ctctagaatg a 1971

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<210> 94
 <211> 656
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 94

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
 260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
 275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
 290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
 305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
 325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
 340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
 355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
 370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
 385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
 405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
 420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
 435 440 445

Tyr Gly Gly Phe Leu Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly
 450 455 460

Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Asn Leu
 465 470 475 480

Asp Trp Asp Val Ile Arg Asp Lys Thr Lys Thr Lys Ile Glu Ser Leu
 485 490 495

Lys Glu His Gly Pro Ile Lys Asn Lys Met Ser Glu Ser Pro Asn Lys
500 505 510

Thr Val Ser Glu Glu Lys Ala Lys Gln Tyr Leu Glu Glu Phe His Gln
515 520 525

Thr Ala Leu Glu His Pro Glu Leu Ser Glu Leu Lys Thr Val Thr Gly
530 535 540

Thr Asn Pro Val Phe Ala Gly Ala Asn Tyr Ala Ala Trp Ala Val Asn
545 550 555 560

Val Ala Gln Val Ile Asp Ser Glu Thr Ala Asp Asn Leu Glu Lys Thr
565 570 575

Thr Ala Ala Leu Ser Ile Leu Pro Gly Ile Gly Ser Val Met Gly Ile
580 585 590

Ala Asp Gly Ala Val His His Asn Thr Glu Glu Ile Val Ala Gln Ser
595 600 605

Ile Ala Leu Ser Ser Leu Met Val Ala Gln Ala Ile Pro Leu Val Gly
610 615 620

Glu Leu Val Asp Ile Gly Phe Ala Ala Tyr Asn Phe Val Glu Ser Ile
625 630 635 640

Ile Asn Leu Phe Gln Val Val His Asn Ser Tyr Asn Arg Pro Leu Glu
645 650 655

<210> 95

<211> 1329

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 95

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attactgacc gcatttggat tgttccagag cgttacgagt tcgggacgaa accagaagat 180

tttaaccgcg cttcatcgct gatcgaagga gcatcagagt attacgatcc gaactatctg 240

cgtacggaca gcgataaaga ccgcttotta cagaccatgg tcaaactttt taaccgtatt 300

aagaacaatg tggccggaga agcactottg gataagatta tcaacgcgat tccatacctg 360

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atTTTTggtc caggtcctgt actgaataaa aatgaagtac gcggcatcgt tctccgctg 540
gacaataaga actacttccc atgccgtgac ggcttcggtt cgatcatgca gatggctttc 600
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ctgcacggct tatatggtat gcaagtgtcc tcgcatgaaa tcattccgtc caaacaggaa 780
atttatatgc agcataccta cccgatttca gctgaagagt tgtttacgtt tgggtggccag 840
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accgaaattg agttggggaa gaaatttaac attaaaaccc gtctgtctta ttttagtatg 1140
aaccatgac cggtgaaaat cccaatctg cttgatgata ccatttataa tgataccgaa 1200
gggttcaaca ttgaatctaa ggatctgaaa tccgaatata aaggccaaaa tatgcgtggt 1260
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tgtgtcgac 1329

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<210> 96
<211> 2736
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

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attactgacc gcatttggat tgttccagag cgttacgagt tcgggacgaa accagaagat 180
tttaaccgcg cttcatcgct gatcgaagga gcatcagagt attacgatcc gaactatctg 240
cgtaacggaca gcgataaaga ccgcttctta cagaccatgg tcaaactttt taaccgtatt 300
aagaacaatg tggccggaga agcactcttg gataagatta tcaacgcgat tccatacctg 360
ggcaattctt acagcctgct ggataaattt gacacaaata gtaattcagt cagctttaac 420
ctgttagaac aagatccgag tggcgcaacc acgaagtctg ccatgctgac aaatctgac 480
atTTTTggtc caggtcctgt actgaataaa aatgaagtac gcggcatcgt tctccgctg 540

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gacaataaga actacttccc atgccgtgac ggcttcgggtt cgatcatgca gatggctttc	600
tgtccggagt acgttccgac gtttgataat gttattgaga atatcacgag ttttaacaatc	660
ggtaagtcaa aatatTTTTca agatccggcc cttctcctta tgcatagaact gattcacgtg	720
ctgcacggct tatatggtat gcaagtgtcc tcgcatgaaa tcattccgtc caaacaggaa	780
atTTtatatgc agcatacctt cccgatttca gctgaagagt tgTTttacgtt tggTggccag	840
gacgcgaatt tgatctccat cgacatcaaa aacgatctgt atgagaaaac attaaatgac	900
tataaagcga ttgcgaacaa actgtctcag gtgactagct gcaacgatcc taacattgat	960
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cagtatatcg taaacgaaga taaatttcag atcctgtata acagcattat gtatggcttt	1080
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gggttcaaca ttgaatctaa ggatctgaaa tccgaataca aaggccaaaa tatgcgtgtt	1260
aatactaacg ctttccgtaa tgTTgatggT agTggactcg tctcgaaact gattgggttg	1320
tgtgtcgacg gcatcattac ctccaaaact aaatctctga tagaaggtag atttggcggT	1380
ttcacgggcg cacgcaaatc agcgcgtaaa cgtaagaacc aggcgctagc gggcggtggc	1440
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gttaacaact gggatttatt cttcagcccg agtgaagaca acttcaccaa cgacctgaac	1560
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caggaatttg aacacggcaa atcccgatat gcaactgacta actccgttaa cgaagctctg	1860
ctcaacctcg cccgtgtata caccttcttc tctagcgact acgtgaaaaa ggtcaacaaa	1920
gcgactgaag ctgcaatgtt cttgggttggt gttgaacagc ttgtttatga ttttaccgac	1980
gagacgtccg aagtatctac taccgacaaa attgcggata tcaactatcat catcccgta	2040
atcggTcccg ctctgaacat tggcaacatg ctgtacaaag acgacttcgt tggcgcaactg	2100
atcttctccg gtgcggtgat cctgctggag ttcatcccg aaatcgccat cccggTactg	2160
ggcacctttg ctctggtttc ttacattgca aacaaggTtc tgactgtaca aaccatcgac	2220
aacgcgctga gcaaacgtaa cgaaaaatgg gatgaagTtt acaaatatat cgtgaccaac	2280
tggttggtta aggttaatac tcagatcgac ctcatccgca aaaaaatgaa agaagcactg	2340

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gaaaaccagg cggaagctac caaggcaatc attaactacc agtacaacca gtacaccgag 2400
gaagaaaaaa acaacatcaa cttcaacatc gacgatctgt cctctaaact gaacgaatcc 2460
atcaacaaag ctatgatcaa catcaacaag ttcctgaacc agtgctctgt aagctatctg 2520
atgaactcca tgatcccgta cgggtgttaaa cgtctggagg acttcgatgc gtctctgaaa 2580
gacgccctgc tgaaatacat ttacgacaac cgtggcactc tgatcgggtca ggttgatcgt 2640
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gtcgataacc aacgcctttt gtccactcta gactag 2736

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<210> 97
<211> 911
<212> PRT
<213> Artificial Sequence

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<220>
<223> Synthetic

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<400> 97

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Gly Ser Met Pro Ile Thr Ile Asn Asn Phe Arg Tyr Ser Asp Pro Val
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Asn Asn Asp Thr Ile Ile Met Met Glu Pro Pro Tyr Cys Lys Gly Leu
20           25           30

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Asp Ile Tyr Tyr Lys Ala Phe Lys Ile Thr Asp Arg Ile Trp Ile Val
35           40           45

```

```

Pro Glu Arg Tyr Glu Phe Gly Thr Lys Pro Glu Asp Phe Asn Pro Pro
50           55           60

```

```

Ser Ser Leu Ile Glu Gly Ala Ser Glu Tyr Tyr Asp Pro Asn Tyr Leu
65           70           75           80

```

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Arg Thr Asp Ser Asp Lys Asp Arg Phe Leu Gln Thr Met Val Lys Leu
85           90           95

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Phe Asn Arg Ile Lys Asn Asn Val Ala Gly Glu Ala Leu Leu Asp Lys
100          105          110

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Ile Ile Asn Ala Ile Pro Tyr Leu Gly Asn Ser Tyr Ser Leu Leu Asp
115          120          125

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Lys Phe Asp Thr Asn Ser Asn Ser Val Ser Phe Asn Leu Leu Glu Gln
130          135          140

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Asp Pro Ser Gly Ala Thr Thr Lys Ser Ala Met Leu Thr Asn Leu Ile
 145 150 155 160

Ile Phe Gly Pro Gly Pro Val Leu Asn Lys Asn Glu Val Arg Gly Ile
 165 170 175

Val Leu Arg Val Asp Asn Lys Asn Tyr Phe Pro Cys Arg Asp Gly Phe
 180 185 190

Gly Ser Ile Met Gln Met Ala Phe Cys Pro Glu Tyr Val Pro Thr Phe
 195 200 205

Asp Asn Val Ile Glu Asn Ile Thr Ser Leu Thr Ile Gly Lys Ser Lys
 210 215 220

Tyr Phe Gln Asp Pro Ala Leu Leu Leu Met His Glu Leu Ile His Val
 225 230 235 240

Leu His Gly Leu Tyr Gly Met Gln Val Ser Ser His Glu Ile Ile Pro
 245 250 255

Ser Lys Gln Glu Ile Tyr Met Gln His Thr Tyr Pro Ile Ser Ala Glu
 260 265 270

Glu Leu Phe Thr Phe Gly Gly Gln Asp Ala Asn Leu Ile Ser Ile Asp
 275 280 285

Ile Lys Asn Asp Leu Tyr Glu Lys Thr Leu Asn Asp Tyr Lys Ala Ile
 290 295 300

Ala Asn Lys Leu Ser Gln Val Thr Ser Cys Asn Asp Pro Asn Ile Asp
 305 310 315 320

Ile Asp Ser Tyr Lys Gln Ile Tyr Gln Gln Lys Tyr Gln Phe Asp Lys
 325 330 335

Asp Ser Asn Gly Gln Tyr Ile Val Asn Glu Asp Lys Phe Gln Ile Leu
 340 345 350

Tyr Asn Ser Ile Met Tyr Gly Phe Thr Glu Ile Glu Leu Gly Lys Lys
 355 360 365

Phe Asn Ile Lys Thr Arg Leu Ser Tyr Phe Ser Met Asn His Asp Pro
 370 375 380

Val Lys Ile Pro Asn Leu Leu Asp Asp Thr Ile Tyr Asn Asp Thr Glu

385		390		395		400
Gly Phe Asn Ile Glu Ser Lys Asp Leu Lys Ser Glu Tyr Lys Gly Gln						
		405		410		415
Asn Met Arg Val Asn Thr Asn Ala Phe Arg Asn Val Asp Gly Ser Gly						
		420		425		430
Leu Val Ser Lys Leu Ile Gly Leu Cys Val Asp Gly Ile Ile Thr Ser						
		435		440		445
Lys Thr Lys Ser Leu Ile Glu Gly Arg Phe Gly Gly Phe Thr Gly Ala						
		450		455		460
Arg Lys Ser Ala Arg Lys Arg Lys Asn Gln Ala Leu Ala Gly Gly Gly						
		465		470		475
				475		480
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu						
		485		490		495
Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu						
		500		505		510
Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp						
		515		520		525
Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln						
		530		535		540
Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser						
		545		550		555
				555		560
Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro						
		565		570		575
Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr						
		580		585		590
Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser						
		595		600		605
Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser						
		610		615		620
Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys						
		625		630		635
				635		640

Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr
645 650 655

Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala
660 665 670

Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly
675 680 685

Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly
690 695 700

Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu
705 710 715 720

Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val
725 730 735

Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu
740 745 750

Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln
755 760 765

Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala
770 775 780

Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu
785 790 795 800

Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys
805 810 815

Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu
820 825 830

Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly
835 840 845

Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu
850 855 860

Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg
865 870 875 880

Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln
885 890 895

Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
900 905 910

<210>	98
<211>	180
<212>	DNA
<213>	Artificial Sequence

<220>
<223> Synthetic

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<210> 99
<211> 2715
<212> DNA
<213> Artificial Sequence
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<220>
<223> Synthetic

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aaaaacatcc tgtacctgga tacccatctg aatacccttg cgaacgaacc ggaaaaagcg	120
tttcgtatca ccggcaacat ttgggttatt ccggatcgtt ttagccgtaa cagcaaccgc	180
aatctgaata aaccgccgcg tgttaccagc ccgaaaagcg gttattacga tccgaactat	240
ctgagcaccg atagcgataa agataccttc ctgaaagaaa tcatcaaact gttcaaacgc	300
atcaacagcc gtgaaattgg cgaagaactg atctatcgcc tgagcaccga tattccgttt	360
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attattaccg gtccgcgcga aaacattatt gatccggaaa ccagcacctt taaactgacc	540
aacaacacct ttgcggcgca ggaaggtttt ggcgcgctga gcattattag cattagcccc	600
cgttttatgc tgacctatag caacgcgacc aacgatgttg gtgaaggccg tttcagcaaa	660
agcgaatttt gcatggaccc gatcctgatc ctgatgcatg aactgaacca tgcgatgcat	720
aacctgtatg gcatcgcgat tccgaacgat cagaccatta gcagcgtgac cagcaacatc	780
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tatcgcagca ttgcgaaacg tctgaacagc attaccaccg cgaatccgag cagcttcaac	960
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ctggcgaaca aagttaatgc ggtgttcag ggcgggtctgt ttctgatgtg ggcgaacgat	1920
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Val Ile Pro Asp Arg Phe Ser Arg Asn Ser Asn Pro Asn Leu Asn Lys
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Pro Pro Arg Val Thr Ser Pro Lys Ser Gly Tyr Tyr Asp Pro Asn Tyr
65 70 75 80

Leu Ser Thr Asp Ser Asp Lys Asp Thr Phe Leu Lys Glu Ile Ile Lys
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Leu Phe Lys Arg Ile Asn Ser Arg Glu Ile Gly Glu Glu Leu Ile Tyr
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Arg Leu Ser Thr Asp Ile Pro Phe Pro Gly Asn Asn Asn Thr Pro Ile
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Asn Thr Phe Asp Phe Asp Val Asp Phe Asn Ser Val Asp Val Lys Thr
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Ile Ile Thr Gly Pro Arg Glu Asn Ile Ile Asp Pro Glu Thr Ser Thr
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Phe Lys Leu Thr Asn Asn Thr Phe Ala Ala Gln Glu Gly Phe Gly Ala
180 185 190

Leu Ser Ile Ile Ser Ile Ser Pro Arg Phe Met Leu Thr Tyr Ser Asn
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Ala Thr Asn Asp Val Gly Glu Gly Arg Phe Ser Lys Ser Glu Phe Cys
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Met Asp Pro Ile Leu Ile Leu Met His Glu Leu Asn His Ala Met His
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Asn Leu Tyr Gly Ile Ala Ile Pro Asn Asp Gln Thr Ile Ser Ser Val
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Thr Ser Asn Ile Phe Tyr Ser Gln Tyr Asn Val Lys Leu Glu Tyr Ala
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Ala Arg Lys Tyr Phe Glu Glu Lys Ala Leu Asp Tyr Tyr Arg Ser Ile
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Glu Leu Tyr Asn Glu Leu Thr Gln Ile Phe Thr Glu Phe Asn Tyr Ala
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Lys Ile Tyr Asn Val Gln Asn Arg Lys Ile Tyr Leu Ser Asn Val Tyr
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Thr Pro Val Thr Ala Asn Ile Leu Asp Asp Asn Val Tyr Asp Ile Gln
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Asn Gly Phe Asn Ile Pro Lys Ser Asn Leu Asn Val Leu Phe Met Gly
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Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys Asn
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Thr Asp Leu Pro Phe Ile Gly Asp Ile Ser Asp Val Lys Thr Asp Ile
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Phe Leu Arg Lys Asp Ile Asn Glu Glu Thr Glu Val Ile Tyr Tyr Pro
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Asp Asn Val Ser Val Asp Gln Val Ile Leu Ser Lys Asn Thr Ser Glu
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His Gly Gln Leu Asp Leu Leu Tyr Pro Ser Ile Asp Ser Glu Ser Glu
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Ile Leu Pro Gly Glu Asn Gln Val Phe Tyr Asp Asn Arg Thr Gln Asn
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Val Asp Tyr Leu Asn Ser Tyr Tyr Tyr Leu Glu Ser Gln Lys Leu Ser
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Asp Asn Val Glu Asp Phe Thr Phe Thr Arg Ser Ile Glu Glu Ala Leu
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Asp Asn Ser Ala Lys Val Tyr Thr Tyr Phe Pro Thr Leu Ala Asn Lys
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Val Val Glu Asp Phe Thr Thr Asn Ile Leu Arg Lys Asp Thr Leu Asp
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Lys Ile Ser Asp Val Ser Ala Ile Ile Pro Tyr Ile Gly Pro Ala Leu
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Asn Ile Ser Asn Ser Val Arg Arg Gly Asn Phe Thr Glu Ala Phe Ala
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Val Thr Gly Val Thr Ile Leu Leu Glu Ala Phe Pro Glu Phe Thr Ile
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Pro Ala Leu Gly Ala Phe Val Ile Tyr Ser Lys Val Gln Glu Arg Asn
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Glu Ile Ile Lys Thr Ile Asp Asn Cys Leu Glu Gln Arg Ile Lys Arg
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Trp Lys Asp Ser Tyr Glu Trp Met Met Gly Thr Trp Leu Ser Arg Ile
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Tyr Gln Ala Gly Ala Ile Lys Ala Lys Ile Asp Leu Glu Tyr Lys Lys
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Tyr Ser Gly Ser Asp Lys Glu Asn Ile Lys Ser Gln Val Glu Asn Leu
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Lys Asn Ser Leu Asp Val Lys Ile Ser Glu Ala Met Asn Asn Ile Asn
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Lys Phe Ile Arg Glu Cys Ser Val Thr Tyr Leu Phe Lys Asn Met Leu
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Pro Lys Val Ile Asp Glu Leu Asn Glu Phe Asp Arg Asn Thr Lys Ala
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Lys Leu Ile Asn Leu Ile Asp Ser His Asn Ile Ile Leu Val Gly Glu
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Val Asp Lys Leu Lys Ala Lys Val Asn Asn Ser Phe Gln Asn Thr Ile
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Pro Phe Asn Ile Phe Ser Tyr Thr Asn Asn Ser Leu Leu Lys Asp Ile
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Ile Asn Glu Tyr Phe Asn Leu Asp
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